

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

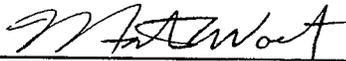
21-398

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

TIME SENSITIVE PATENT INFORMATION

DECLARATION

Pursuant to Sections 505(b) and (c) of the Federal Food Drug and Cosmetic Act (Act), and 21 C.F.R. §314.53, the undersigned declares that U.S. Patent No. 6,194,415 B1 ("the '415 patent") covers the method of use of Brimonidine Tartrate 0.2%/Timolol 0.5% ophthalmic solution. This product is the subject of this application for which approval is being sought.

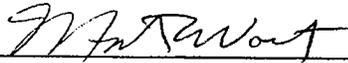


Martin Voet
Vice President
Chief Intellectual Property Counsel
Allergan, Inc.
2525 Dupont Drive
Irvine, CA 92612-1599
Telephone: 714 - 246-5894

TIME SENSITIVE PATENT INFORMATION

DECLARATION

Pursuant to Sections 505(b) and (c) of the Federal Food Drug and Cosmetic Act (Act), and 21 C.F.R. §314.53, the undersigned declares that U.S. Patent No. 6,248,741 B1 ("the '741 patent") covers the method of use of Brimonidine Tartrate 0.2%/Timolol 0.5% ophthalmic solution. This product is the subject of this application for which approval is being sought.



Martin Voet
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2525 Dupont Drive
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14. CERTIFICATION FOR EXCLUSIVITY

Allergan, Inc. (the applicant) is submitting information in support of a request for three-year exclusivity per Section 505 (c)(3)(D) and 505 (j)(4)(D) of the Federal Food, Drug, and Cosmetic Act for Brimonidine Tartrate 0.2%/Timolol 0.5% Combination Product NDA. The results of the following two controlled clinical studies demonstrate that Brimonidine Tartrate 0.2%/Timolol 0.5% Combination Product is safe and efficacious for the lowering of intraocular pressure in patients with  glaucoma or ocular hypertension. In the applicant's opinion, these studies are essential to the approval of the new drug application for Brimonidine Tartrate 0.2%/Timolol 0.5% Combination Product. The applicant is the sponsor of IND 58,460 under which these clinical studies were conducted:

190342-012T

A multicenter, double-masked, randomized, parallel study of the safety and efficacy of 0.2% Brimonidine tartrate / 0.5% Timolol combination ophthalmic solution twice-daily compared with 0.5% Timolol twice-daily or ALPHAGAN® three-times daily for three months (plus 9-month, masked extension) in patients with glaucoma or ocular hypertension.

190342-013T

A multicenter, double-masked, randomized, parallel study of the safety and efficacy of 0.2% Brimonidine tartrate / 0.5% Timolol combination ophthalmic solution twice-daily compared with 0.5% Timolol twice-daily or ALPHAGAN® three-times daily for three months (plus 9-month, masked extension) in patients with glaucoma or ocular hypertension.

Allergan, Inc. (the applicant) has also submitted information in support of a request for an additional six month extension of exclusivity per Section 505A(d) of the Federal Food, Drug, and Cosmetic Act for Brimonidine Tartrate 0.2%/Timolol 0.5% Combination Product. A clinical study report was submitted to NDA 20-613 on August 14, 2001 in response to a June 25, 1999 FDA Written Request to determine if the use of the drug could have meaningful health benefits in the pediatric population. The applicant is the sponsor of IND 32,292 under which this clinical study was conducted:

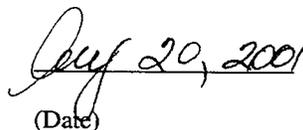
190342-015

A 3-month, multicenter, randomized, double-masked, parallel comparison of the safety, efficacy, and tolerability of ALPHAGAN® TID vs. TRUSOPT® TID as adjunctive treatment to ophthalmic beta-blocker treatment in pediatric glaucoma patients.

Allergan, Inc., hereby certifies that to the best of our knowledge, the clinical investigations listed herein have not formed part of the basis of a finding of substantial evidence of effectiveness for a previously approved new drug application or supplement. Furthermore, no other drug product containing all of the same ingredients with the same conditions of approval has been previously approved for human use. The scientific literature has been thoroughly searched and in the applicant's opinion there are no published studies or publicly available reports of clinical investigations (other than those sponsored by the applicant) to support the approval of the new drug application for Brimonidine Tartrate 0.2%/Timolol 0.5% Combination Product. The applicant is not aware of any approvals of this product for human use.



Peter A. Kresel, MS, MBA
Sr. Vice President, Global Regulatory Affairs
Allergan, Inc.



(Date)

Department of Health and Human Services
Food and Drug Administration

Form Approved: OMB No. 0910-0513
Expiration Date: 07/31/06
See OMB Statement on Page 3.

**PATENT INFORMATION SUBMITTED WITH THE
FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT**

**For Each Patent That Claims a Drug Substance
(Active Ingredient), Drug Product (Formulation and
Composition) and/or Method of Use**

NDA NUMBER

21-398

NAME OF APPLICANT / NDA HOLDER

Allergan, Inc.

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)

COMBIGAN

ACTIVE INGREDIENT(S)

brimonidine tartrate / timolol maleate

STRENGTH(S)

0.2% / 0.5%

DOSAGE FORM

ophthalmic solution

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number

6,194,415

b. Issue Date of Patent

2/27/2001

c. Expiration Date of Patent

6/28/2015

d. Name of Patent Owner

Allergan, Inc.

Address (of Patent Owner)

2525 Dupont Drive

City/State

Irvine, CA

ZIP Code

92612

FAX Number (if available)

714 246 4272

Telephone Number

714 246 6088

E-Mail Address (if available)

gryziewicz_lewis@allergan.com

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

Address (of agent or representative named in 1.e.)

City/State

ZIP Code

FAX Number (if available)

Telephone Number

E-Mail Address (if available)

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?

Yes

No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?

Yes

No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

- 2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement? Yes No
- 2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement? Yes No
- 2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b). Yes No

2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.

2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.) Yes No

2.6 Does the patent claim only an intermediate? Yes No

2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement? Yes No

3.2 Does the patent claim only an intermediate? Yes No

3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

4.2 Patent Claim Number (as listed in the patent) 1,2,5 Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product. Use: (Submit indication or method of use information as identified specifically in the approved labeling.)

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. Yes

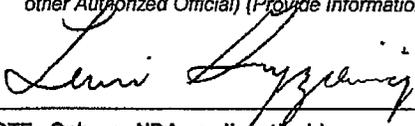
6. Declaration Certification

3.1 The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)

Date Signed



7 / 26 / 06

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

NDA Applicant/Holder

NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official

Patent Owner

Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name
Allergan, Inc.

Address
2424 Dupont Drive

City/State
Irvine, CA

ZIP Code
92612

Telephone Number
714 246 6088

FAX Number (if available)
714 246 4272

E-Mail Address (if available)
gryziewicz_lewis@allergan.com

The public reporting burden for this collection of information has been estimated to average 9 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration
CDER (HFD-007)
5600 Fishers Lane
Rockville, MD 20857

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

**PATENT INFORMATION SUBMITTED WITH THE
FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT**
*For Each Patent That Claims a Drug Substance
(Active Ingredient), Drug Product (Formulation and
Composition) and/or Method of Use*

NDA NUMBER

21-398

NAME OF APPLICANT / NDA HOLDER

Allergan, Inc.

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)
COMBIGAN

ACTIVE INGREDIENT(S)
brimonidine tartrate / timolol maleate

STRENGTH(S)
0.2% / 0.5%

DOSAGE FORM
ophthalmic solution

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number
6,248,741

b. Issue Date of Patent
6/19/2001

c. Expiration Date of Patent
6/28/2015

d. Name of Patent Owner
Allergan, Inc.

Address (of Patent Owner)
2525 Dupont Drive

City/State
Irvine, CA

ZIP Code
92612

FAX Number (if available)
714 246 4272

Telephone Number
714 246 6088

E-Mail Address (if available)
gryziewicz_lewis@allergan.com

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

Address (of agent or representative named in 1.e.)

City/State

ZIP Code

FAX Number (if available)

Telephone Number

E-Mail Address (if available)

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?

Yes No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?

Yes No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

- 2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement? Yes No
- 2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement? Yes No
- 2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b). Yes No

2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.

- 2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.) Yes No
- 2.6 Does the patent claim only an intermediate? Yes No
- 2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

3. Drug Product (Composition/Formulation)

- 3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement? Yes No
- 3.2 Does the patent claim only an intermediate? Yes No
- 3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

- 4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No
- 4.2 Patent Claim Number (as listed in the patent) 1,2,3,11 Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.

Use: (Submit indication or method of use information as identified specifically in the approved labeling.)

~~_____~~

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. Yes

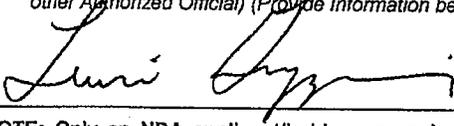
6. Declaration Certification

6.1 The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)

Date Signed



7/26/06

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

NDA Applicant/Holder

NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official

Patent Owner

Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name
Allergan, Inc.

Address
2424 Dupont Drive

City/State
Irvine, CA

ZIP Code
92612

Telephone Number
714 246 6088

FAX Number (if available)
714 246 4272

E-Mail Address (if available)
gryziewicz_lewis@allergan.com

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Food and Drug Administration
CDER (HFD-007)
5600 Fishers Lane
Rockville, MD 20857

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Department of Health and Human Services
Food and Drug Administration

Form Approved: OMB No. 0910-0513
Expiration Date: 07/31/06
See OMB Statement on Page 3.

**PATENT INFORMATION SUBMITTED WITH THE
FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT**

**For Each Patent That Claims a Drug Substance
(Active Ingredient), Drug Product (Formulation and
Composition) and/or Method of Use**

NDA NUMBER

21-398

NAME OF APPLICANT / NDA HOLDER

Allergan, Inc.

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)

COMBIGAN

ACTIVE INGREDIENT(S)

brimonidine tartrate / timolol maleate

STRENGTH(S)

0.2% / 0.5%

DOSAGE FORM

ophthalmic solution

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4).

Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

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For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number

7,030,149

b. Issue Date of Patent

4/18/2006

c. Expiration Date of Patent

4/19/2022

d. Name of Patent Owner

Allergan, Inc.

Address (of Patent Owner)

2525 Dupont Drive

City/State

Irvine, CA

ZIP Code

92612

FAX Number (if available)

714 246 4272

Telephone Number

714 246 6088

E-Mail Address (if available)

gryziewicz_lewis@allergan.com

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

Address (of agent or representative named in 1.e.)

City/State

ZIP Code

FAX Number (if available)

Telephone Number

E-Mail Address (if available)

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?

Yes

No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?

Yes

No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	<input type="checkbox"/> Yes	<input type="checkbox"/> No
2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.		
2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
2.6 Does the patent claim only an intermediate?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	<input type="checkbox"/> Yes	<input type="checkbox"/> No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
3.2 Does the patent claim only an intermediate?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	<input type="checkbox"/> Yes	<input type="checkbox"/> No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No
4.2 Patent Claim Number (as listed in the patent) 1-4	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?	
	<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: (Submit indication or method of use information as identified specifically in the approved labeling.) COMBIGAN (brimonidine tartrate 0.2% / timolol 0.5% ophthalmic solution) is indicated for reduction of elevated intraocular pressure in patients with glaucoma or ocular hypertension who require adjunctive or replacement therapy due to inadequately controlled IOP.	

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. Yes

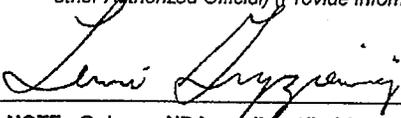
6. Declaration Certification

6.1 The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.

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6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)

Date Signed



7/26/06

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

NDA Applicant/Holder

NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official

Patent Owner

Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name
Allergan, Inc.

Address
2424 Dupont Drive

City/State
Irvine, CA

ZIP Code
92612

Telephone Number
714 246 6088

FAX Number (if available)
714 246 4272

E-Mail Address (if available)
gryziewicz_lewis@allergan.com

The public reporting burden for this collection of information has been estimated to average 9 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration
CDER (HFD-007)
5600 Fishers Lane
Rockville, MD 20857

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

EXCLUSIVITY SUMMARY

NDA # 21-398

SUPPL #

HFD # 520

Trade Name COMBIGAN

Generic Name brimonidine tartrate/timolol maleate ophthalmic solution

Applicant Name Allergan, Inc.

Approval Date, If Known 10-26-07

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)(2)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 18-086, 19-463 Timolol Maleate

NDA# 20-613 Alphagan

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of

summary for that investigation.

YES NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

190342-012T: A Multicenter, Double-Masked, Randomized, Parallel Study of the Safety and Efficacy of 0.2% Brimonidine Tartrate/0.5% Timolol Combination Ophthalmic Solution Twice-daily Compared with 0.5% Timolol Twice-Daily or ALPHAGAN Three-Times-Daily for Three Months (Plus 9-Months, Masked Extension) in Patients with Glaucoma or Ocular Hypertension

190342-013T: A Multicenter, Double-Masked, Randomized, Parallel Study of the Safety and Efficacy of 0.2% Brimonidine Tartrate/0.5% Timolol Combination Ophthalmic Solution Twice-Daily Compared with 0.5% Timolol Twice-Daily or Extension) in Patients with Glaucoma or Ocular Hypertension

190342-019T: A Multi-Center, Double-masked, Randomized, Parallel, Four-Week Study of the Safety and Efficacy of 0.2% Brimonidine Tartrate/0.5% Timolol Combination Ophthalmic Solution BID Compared with Concurrent, ALPHAGAN TID and TIMOLOL BID (0.2% Brimonidine Tartrate and 0.5% TIMOLOL) Ophthalmic Solutions and ALPHAGAN (0.2% Brimonidine Tartrate) Ophthalmic Solution TID in Treatment-Naive Patients with Glaucoma or Ocular Hypertension

190342-023T: A Multi-Center, Randomized, Double-Masked, Parallel-Group Study to Evaluate the Safety of BID (Twice-Daily) Administration of 0.2% Brimonidine Tartrate/0.5% Timolol Fixed Combination Ophthalmic Solution Compared with ALPHAGAN (0.2% Brimonidine Tartrate) TID (Three Times Daily) and 0.5% Timolol BID Given Concurrently in Healthy, Adult Subjects for Ten Day

190342-024T : A Multi-Center, Randomized, Double-Masked, Parallel-Group Study to Evaluate the Safety of BID (Twice-Daily) Administration of 0.2% Brimonidine Tartrate 0.5% Timolol Fixed Combination Ophthalmic Solution Compared with Alphagan (0.2% Brimonidine Tartrate) TID (Three Times Daily) and 0.5% Timolol BID Given Concurrently in Glaucoma or Ocular Hypertension Patients for Ten Days

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the

effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 - 5 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 - 5 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

190342-012T: A Multicenter, Double-Masked, Randomized, Parallel Study of the Safety and Efficacy of 0.2% Brimonidine Tartrate/0.5% Timolol Combination Ophthalmic Solution Twice-daily Compared with 0.5% Timolol Twice-Daily or ALPHAGAN Three-Times-Daily for Three Months (Plus 9-Months, Masked Extension) in Patients with Glaucoma or Ocular Hypertension

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Hypertension

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190342-024T : A Multi-Center, Randomized, Double-Masked, Parallel-Group Study to Evaluate the Safety of BID (Twice-Daily) Administration of 0.2% Brimonidine Tartrate 0.5% Timolol Fixed Combination Ophthalmic Solution Compared with Alphagan (0.2% Brimonidine Tartrate) TID (Three Times Daily) and 0.5% Timolol BID Given Concurrently in Glaucoma or Ocular Hypertension Patients for Ten Days

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !
!
IND # 58,460 YES ! NO
! Explain:

Investigation #2 !
!
IND # YES ! NO
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

**Appears This Way
On Original**

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

DA/BLA #: 21-398 Supplement Type (e.g. SE5): _____ Supplement Number: _____

Stamp Date: May 3, 2007 PDUFA Goal Date: November 2, 2007

HFD 520 Trade and generic names/dosage form: COMBIGAN™ (brimonidine tartrate/timolol maleate ophthalmic solution) 0.2%/0.5%

Applicant: Allergan, Inc. Therapeutic Class: alpha-agonist/beta-blocker

Does this application provide for new active ingredient(s), new indication(s), new dosage form, new dosing regimen, or new route of administration? *

- Yes. Please proceed to the next question.
 No. PREA does not apply. Skip to signature block.

* SE5, SE6, and SE7 submissions may also trigger PREA. If there are questions, please contact the Rosemary Addy or Grace Carmouze.

Indication(s) previously approved (please complete this section for supplements only): _____

Each indication covered by current application under review must have pediatric studies: *Completed, Deferred, and/or Waived.*

Number of indications for this application(s): 1

Indication #1: Reduction of elevated intraocular pressure (IOP) in patients with glaucoma or ocular hypertension who require adjunctive or replacement therapy due to inadequately controlled IOP.

Is this an orphan indication?

- Yes. PREA does not apply. Skip to signature block.
 No. Please proceed to the next question.

Is there a full waiver for this indication (check one)?

- Yes: Please proceed to Section A.
 No: Please check all that apply: Partial Waiver Deferred Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
 Disease/condition does not exist in children
 Too few children with disease to study
 There are safety concerns
 Other: _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived (fill in applicable criteria below):

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred (fill in applicable criteria below):

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed

Other: _____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies (fill in applicable criteria below):

Min _____ kg _____ mo. _____ yr. 2 Tanner Stage _____
Max _____ kg _____ mo. _____ yr. N/A Tanner Stage _____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

NDA 21-398

Page 3

This page was completed by:

{See appended electronic signature page}

Alison Rodgers

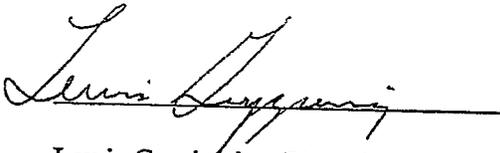
Regulatory Project Manager

**FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH
STAFF at 301-796-0700**

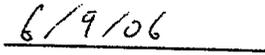
(Revised: 10/10/2006)

16. Debarment Certification

Allergan, Inc. hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.



Lewis Gryziewicz, PharmD
Senior Director
Regulatory Affairs
Allergan, Inc.



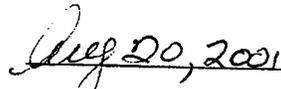
Date

16. DEBARMENT CERTIFICATION

Allergan, Inc., hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.



Peter A. Kresel, MS, MBA
Sr. Vice President, Global Regulatory Affairs
Allergan, Inc.



(Date)

DEPARTMENT OF HEALTH AND HUMAN SERVICES Food and Drug Administration CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS	Form Approved: OMB No. 0910-0396 Expiration Date: April 30, 2009.
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TO BE COMPLETED BY APPLICANT

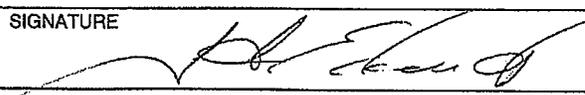
With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

- (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators	see list attached	

- (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).
- (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME Jeff Edwards	TITLE Executive Vice President, Finance and Business Development, Chief Financial Officer
FIRM / ORGANIZATION Allergan, Inc.	
SIGNATURE 	DATE 6-13-06

Paperwork Reduction Act Statement

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Department of Health and Human Services
 Food and Drug Administration
 5600 Fishers Lane, Room 14C-03
 Rockville, MD 20857

1 Page(s) Withheld

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Deliberative Process

DEPARTMENT OF HEALTH AND HUMAN SERVICES Food and Drug Administration DISCLOSURE: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS	Form Approved: OMB No. 0910-0396 Expiration Date: April 30, 2009
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TO BE COMPLETED BY APPLICANT

The following information concerning _____, who participated as a clinical investigator in the submitted study _____, is submitted in accordance with 21 CFR part 54. The named individual has participated in financial arrangements or holds financial interests that are required to be disclosed as follows:

Please mark the applicable checkboxes.

- any financial arrangement entered into between the sponsor of the covered study and the clinical investigator involved in the conduct of the covered study, whereby the value of the compensation to the clinical investigator for conducting the study could be influenced by the outcome of the study;
- any significant payments of other sorts made on or after February 2, 1999 from the sponsor of the covered study such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria;
- any proprietary interest in the product tested in the covered study held by the clinical investigator;
- any significant equity interest as defined in 21 CFR 54.2(b), held by the clinical investigator in the sponsor of the covered study.

Details of the individual's disclosable financial arrangements and interests are attached, along with a description of steps taken to minimize the potential bias of clinical study results by any of the disclosed arrangements or interests.

NAME Jeff Edwards	TITLE Executive Vice President, Finance and Business Development, Chief Financial Officer
FIRM / ORGANIZATION Allergan, Inc.	
SIGNATURE 	DATE 6-13-06

Paperwork Reduction Act Statement

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 5600 Fishers Lane, Room 14-72
 Rockville, MD 20857

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Withheld Track Number: Administrative- 17

DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service Food and Drug Administration	Form Approved: OMB No. 0910-0396 Expiration Date: 3/31/02						
CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS							
TO BE COMPLETED BY APPLICANT							
With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).							
Please mark the applicable checkbox.							
<input checked="" type="checkbox"/> (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).							
Clinical Investigators	<table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 50%; text-align: center;">List Attached</td> <td style="width: 50%;"></td> </tr> <tr> <td style="height: 20px;"></td> <td></td> </tr> <tr> <td style="height: 20px;"></td> <td></td> </tr> </table>	List Attached					
List Attached							
<input type="checkbox"/> (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).							
<input type="checkbox"/> (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.							
NAME Eric Brandt	TITLE Corporate Vice President and Chief Financial Officer						
FIRM/ORGANIZATION Allergan, Inc.							
SIGNATURE 	DATE 8/30/01						
Paperwork Reduction Act Statement							
An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:	Department of Health and Human Services Food and Drug Administration 5600 Fishers Lane, Room 14C-03 Rockville, MD 20857						

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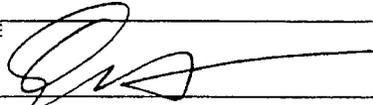
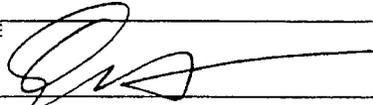
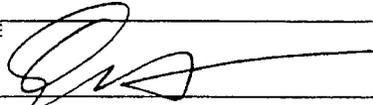
DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service Food and Drug Administration	Form Approved: OMB No. 0910-0396 Expiration Date: 3/31/02
DISCLOSURE: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS	
<i>TO BE COMPLETED BY APPLICANT</i>	
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NAME Eric Brandt	TITLE Corporate Vice President and Chief Financial Officer
FIRM/ORGANIZATION Allergan, Inc.	
SIGNATURE 	DATE 8/20/01
Paperwork Reduction Act Statement	
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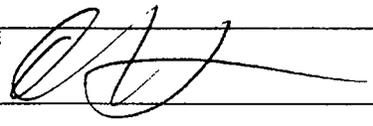
DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service Food and Drug Administration	Form Approved: OMB No. 0910-0396 Expiration Date: 3/31/02						
DISCLOSURE: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS							
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FORM FDA 3455 (7/01)

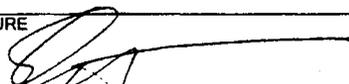
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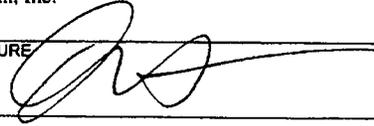
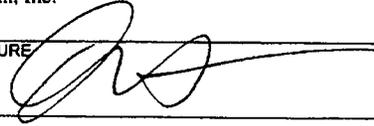
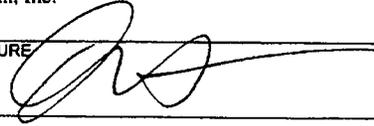
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MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: June 8, 2007

TO: File

FROM: Alison Rodgers

SUBJECT: **NDA 21-398 Resubmission May 2, 2007**
NDA 21-398, COMBIGAN (brimonidine tartrate/timolol maleate
ophthalmic solution)

The May 2, 2007, resubmission of NDA 21-398 is acceptable from a project management standpoint.

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

/s/

Alison Rodgers
6/8/2007 02:53:22 PM
CSO

Rodgers, Alison

From: Rodgers, Alison
Sent: Wednesday, June 06, 2007 12:54 PM
To: 'Gryziewicz_Lewis'
Subject: RE: NDA 21-398 - Request for Information

Hi Lew,

Listed below is our statistician's response to your request for clarification. I hope this helps. Please let me know if you need more information.

The programs outlined in 1. are adequate. Our intention is to reproduce the results and examine how they were created. The operating system is MS Windows 2000 with SAS Version 8.

Alison

Alison K. Rodgers
Regulatory Health Project Manager
FDA/CDER
Division of Anti-Infective and Ophthalmology Products
Phone: 301-796-0797
Fax: 301-796-9882
Email: alison.rodgers@fda.hhs.gov

From: Gryziewicz_Lewis [mailto:Gryziewicz_Lewis@Allergan.com]
Sent: Tuesday, June 05, 2007 5:40 PM
To: Rodgers, Alison
Subject: FW: NDA 21-398 - Request for Information

Alison,

In response to your request we are seeking clarification on what the FDA Statistician expects to receive for the Combigan 024T study. Could you respond to our questions listed below? If necessary we could discuss on the phone with the Statistician.

Thanks,

Lew

1. We will send the programs that create analysis data sets for the primary and secondary analyses as well as the programs that create the tables for these analyses. These tables are listed. Are these the programs that are requested?

Current Severity of Sleepiness

14.3-2.1	Proportion of Sleepiness Responders
14.3-2.2	Proportion of Patients with an Increase of ≥ 2 Units at Each Visit and Overall
14.3-2.3	Frequency Distribution

6/6/2007

14.3-2.4 Baseline and Change from Baseline

Current Severity of Dry Mouth

- 14.3-3.1 Proportion of Dry Mouth Responders
- 14.3-3.2 Proportion of Patients with an Increase of ≥ 1 Units at Each Visit and Overall
- 14.3-3.3 Frequency Distribution
- 14.3-3.4 Baseline and Change from Baseline

Current Severity of Sleepiness in Patients < 65 Years Old

- 14.3-4.1 Proportion of Sleepiness Responders
- 14.3-4.2 Proportion of Patients with an Increase of ≥ 2 Units at Each Visit and Overall
- 14.3-4.3 Frequency Distribution
- 14.3-4.4 Baseline and Change from Baseline

Inappropriate Sleepiness

- 14.3-5.1 Proportion of Responders
- 14.3-5.2 Proportion of Patients with an Increase of ≥ 1 Units at Each Visit and Overall
- 14.3-5.3 Frequency Distribution
- 14.3-5.4 Baseline and Change from Baseline

Sensitivity Analyses of Current Severity of Sleepiness

- 14.6-16.1 Current Severity of Sleepiness: Chi-Square Sensitivity Analysis
- 14.6-16.2 Current Severity of Sleepiness: Sensitivity Analysis Population

2. Is the intention for the FDA to run the programs or to look at the coding logic? Our programs have been written for the UNIX operating system.
3. If the FDA will be running the programs:
 - a. What operating system will be used?
 - b. What version of SAS will be used?

From: Rodgers, Alison [mailto:Alison.Rodgers@fda.hhs.gov]
Sent: Tuesday, June 05, 2007 6:29 AM
To: Gryziewicz_Lewis
Subject: NDA 21-398 - Request for Information

Hi Lew,

Please see below a request from our statistician. Please submit your response to the NDA. Please let me know when you plan to respond. Let me know if you have any questions.

We request that the Sponsor include SAS programs used in conducting the primary analyses, related

sensitivity analyses and secondary analyses for Study 190342-024T.

Also, I did receive your message about submitting the carton and container labeling today. That's fine.

Thanks,

Alison

Alison K. Rodgers
Regulatory Health Project Manager
FDA/CDER
Division of Anti-Infective and Ophthalmology Products
Phone: 301-796-0797
Fax: 301-796-9882
Email: alison.rodgers@fda.hhs.gov

6/6/2007

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/s/

Alison Rodgers
6/6/2007 12:58:12 PM
CSO

Alison Rodgers
6/6/2007 12:58:41 PM
CSO



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-398

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

Dear Dr. Gryziewicz:

We acknowledge receipt on May 3, 2007 of your May 2, 2007 resubmission to your new drug application for COMBIGAN™ (brimonidine tartrate/timolol maleate ophthalmic solution) 0.2%/0.5%.

We consider this a complete, class 2 response to our December 20, 2006 action letter. Therefore, the user fee goal date is November 3, 2007.

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

Sincerely,

{See appended electronic signature page}

Maureen P. Dillon-Parker
Chief, Project Management Staff
Division of Anti-Infective and
Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

Alison Rodgers
5/15/2007 02:37:52 PM

Maureen Dillon-Parker
5/16/2007 08:40:37 AM
NDA 21-398; Ack Ltr Resubmission

**MEMORANDUM
SERVICES**

DEPARTMENT OF HEALTH AND HUMAN

**PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND
RESEARCH**

CLINICAL INSPECTION SUMMARY

DATE: November 14, 2006

TO: Alison Rodgers, Regulatory Project Manager
Jennifer Harris, M.D., Clinical Reviewer
Division of Anti-Infective and Ophthalmology Products, HFD-520

THROUGH: Leslie K. Ball, M.D.
Branch Chief
Good Clinical Practice Branch 2, HFD-47
Division of Scientific Investigations

FROM: Dianne Tesch, Consumer Safety Officer

SUBJECT: Evaluation of Clinical Inspections

NDA: 21-398

NME: No

APPLICANT: Allergan, Inc.

DRUG: Combigan™ (brimonidine tartrate 0.2% / timolol 0.5%) Ophthalmic Solution

THERAPEUTIC CLASSIFICATION: 4S

INDICATION: _____

CONSULTATION REQUEST DATE: July 26, 2006

DIVISION ACTION GOAL DATE: 11/20/06

PDUFA DATE: 12/29/06

I. BACKGROUND:

Glaucoma refers to a group of eye diseases characterized by an increase in the intraocular pressure (IOP) which causes pathological changes in the optic disc and defects in the field of vision. It affects one person in 200 over the age of 40. It is the leading cause of irreversible blindness in the United States. Glaucoma causes a progressive loss of retinal nerve fibers, resulting in vision loss. The various types of glaucoma are distinguished by the causative physiological defect.

Treatment of glaucoma consists of both medical and surgical interventions. The treatments are designed to decrease the intra-ocular pressure by decreasing aqueous secretion, or increasing aqueous outflow.

Timolol ophthalmic solution 0.5%, a non-selective beta-blocker, and brimonidine ophthalmic solution (ALPHAGAN®) 0.2%, a selective and potent alpha-2 adrenoceptor agonist, have both been shown to effectively reduce IOP. Because timolol and brimonidine have different sites of action and different mechanisms by which they lower IOP, it is reasonable to expect that there will be an added IOP lowering effect when the 2 medications are used adjunctively.

Currently, the 2 marketed medications are often prescribed and used together, but this requires that the patient must have 2 separate bottles of medications and results in a cumbersome dosing regimen. Use of 2 separate bottles requires patients to dose 5 drops per eye per day with a 5 minute wait in-between dosing of the 2 bottles. Reducing the number of drops per eye per day may improve dosing compliance. The sponsor has combined these 2 ocular hypotensive medications into a single formulation to provide the benefit of adjunctive therapy with a more convenient dosing regimen (ie, one drop in each eye twice daily).

Dr. McCormack's site was chosen for inspection because of high enrollment, and because he has never been inspected.

Summary Report of U.S. Inspections

II. RESULTS (by protocol/site):

Name of CI and site #, if known	City, State*	Protocol #	Insp. Date	EIR Received Date	Final Classification
Donald L. McCormack	Boulder, CO	190342-023T-00	Oct. 10-18, 2006	Nov. 7, 2006	NAI

*If international site, please insert column for country.

Key to Classifications

NAI = No deviation from regulations. Data acceptable.

VAI-No Response Requested= Deviations(s) from regulations. Data acceptable.

VAI-Response Requested = Deviation(s) from regulations. See specific comments below for data acceptability

OAI = Significant deviations for regulations. Data unreliable.

A. Protocol #190342-023T-00 "A Multi-Center, Randomized, Double-Masked, Parallel-Group Study to Evaluate the Safety of BID (Twice-Daily) Administration of 0.2% Brimonidine Tartrate / 0.5% Timolol Fixed Combination Ophthalmic Solution Compared with ALPHAGAN® (0.2% Brimonidine Tartrate) TID (Three Times Daily) and 0.5% Timolol BID Given Concurrently in Healthy, Adult Subjects for Ten Days"

1. Donald L. McCormack, Boulder, CO; site 1942:
 - a. Fifty-eight subjects were enrolled in this clinical study. Forty-nine were randomized. Forty-eight subjects completed the study. One withdrew consent after experiencing an adverse event. All subject files were reviewed for compliance with eligibility requirements, informed consent, and drug accountability. Twenty-seven subjects' records were reviewed in depth for accuracy of reporting of endpoint data.
 - b. There were no limitations to the inspection.
 - c. There were minor clerical errors in the record keeping. No significant regulatory deficiencies were found.

- d. The study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

There were minor clerical errors at this site which did not affect the integrity or reliability of the data submitted in support of subject NDA or significant patient safety issues.

No follow-up other than routine surveillance is indicated.

{ See appended electronic signature page }

Dianne Tesch, Consumer Safety Officer

CONCURRENCE:

Supervisory comments

{ See appended electronic signature page }

Leslie K. Ball, M.D.
Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations

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/s/

Dianne Tesch
11/16/2006 09:15:39 AM
CSO

Leslie Ball
11/20/2006 08:17:50 PM
MEDICAL OFFICER

Rodgers, Alison

From: Rodgers, Alison
Sent: Wednesday, October 18, 2006 2:39 PM
To: 'Gryziewicz_Lewis'
Subject: NDA 21-398 - CMC Comments

Hi Lew,

Please see CMC comments below regarding NDA 21-398. Please submit your response to the NDA, and send an electronic copy to me, if possible. Also, please let me know when you will respond.

Thank you.

NDA 21-398 COMBIGAN(Brimonidine Tartrate 0.2% / Timolol 0.5%) Ophthalmic Solution

These comments are being provided to you prior to completion of our review of the application to give you preliminary notice of issues that have been identified. Per the user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and are subject to change as the review of your application is finalized. In addition, we may identify other information that must be provided prior to approval of this application. Depending on the timing of your response, as per user fee reauthorization agreements, we may or may not be able to consider your response prior to taking an action on your application during this review cycle.

If your response can be found in the contents of your submission, just cite those sections of the submission that are relevant to the issue under consideration. Otherwise, provide the appropriate information. Your response should be submitted as an amendment to the submission and a copy via facsimile to the reviewer.

CMC COMMENTS

- _____
2. If yes, please revise the "Analytical Procedure for Brimonidine Tartrate, Timolol, and Their Impurities" to include the _____
 3. Although the formation of _____ is attributed to _____ it is conceivable that this is a result of a reaction of _____ . Were preformulation studies conducted to study the _____ . Please provide a study report or reference to such a study in your application.

Alison K. Rodgers
Regulatory Health Project Manager
FDA/CDER
Division of Anti-Infective and Ophthalmology Products
Phone: 301-796-0797
Fax: 301-796-9882
Email: alison.rodgers@fda.hhs.gov

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/s/

Alison Rodgers
10/18/2006 02:48:27 PM
CSO

Alison Rodgers
10/18/2006 02:48:55 PM
CSO

NDA REGULATORY FILING REVIEW (Including Memo of Filing Meeting)

NDA # 21-398 Supplement # Efficacy Supplement Type SE-

Proprietary Name: COMBIGAN™
Established Name: brimonidine tartrate/timolol maleate ophthalmic solution
Strengths: 0.2%/0.5%

Applicant: Allergan, Inc.
Agent for Applicant (if applicable):

Date of Application: 6-29-06
Date of Receipt: 6-30-06
Date clock started after UN:
Date of Filing Meeting: 7-25-06
Filing Date: N/A (This is a resubmission.)
Action Goal Date (optional): User Fee Goal Date: 12-30-06

Indication(s) requested: Reduction of elevated intraocular pressure in patients with glaucoma or ocular hypertension

Type of Original NDA: (b)(1) (b)(2) X
AND (if applicable)
Type of Supplement: (b)(1) (b)(2)

NOTE:

(1) If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application or efficacy supplement is a (b)(2), complete Appendix B.

Review Classification: S X P
Resubmission after withdrawal? Resubmission after refuse to file?
Chemical Classification: (1,2,3 etc.) 4
Other (orphan, OTC, etc.)

Form 3397 (User Fee Cover Sheet) submitted: YES N/A NO

User Fee Status: N/A Paid Exempt (orphan, government)
Waived (e.g., small business, public health)

NOTE: If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required by contacting the User Fee staff in the Office of Regulatory Policy. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx-to-OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the product described in the application.

Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the User Fee staff.

- Is there any 5-year or 3-year exclusivity on this active moiety in any approved (b)(1) or (b)(2) application?
If yes, explain: YES NO

Note: If the drug under review is a 505(b)(2), this issue will be addressed in detail in appendix B.

- Does another drug have orphan drug exclusivity for the same indication? YES NO
- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? YES NO

If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)?
If yes, explain: YES NO
- If yes, has OC/DMPQ been notified of the submission? YES NO
- Does the submission contain an accurate comprehensive index?
If no, explain: YES NO
- Was form 356h included with an authorized signature?
If foreign applicant, both the applicant and the U.S. agent must sign. YES NO
- Submission complete as required under 21 CFR 314.50?
If no, explain: YES NO

- Answer 1, 2, or 3 below (do not include electronic content of labeling as an partial electronic submission).

1. This application is a paper NDA YES
2. This application is an eNDA or combined paper + eNDA YES
This application is: All electronic Combined paper + eNDA
This application is in: NDA format CTD format
Combined NDA and CTD formats

Does the eNDA, follow the guidance?
(<http://www.fda.gov/cder/guidance/2353fml.pdf>) YES NO

If an eNDA, all forms and certifications must be in paper and require a signature.

If combined paper + eNDA, which parts of the application were submitted in electronic format?

Additional comments:

3. This application is an eCTD NDA. YES

If an eCTD NDA, all forms and certifications must either be in paper and signed or be electronically signed.

Additional comments:

- Patent information submitted on form FDA 3542a? YES X NO
- Exclusivity requested? YES, _____ Years NO X
NOTE: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.
- Correctly worded Debarment Certification included with authorized signature? YES X NO
If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

NOTE: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as "To the best of my knowledge"

- Are the required pediatric assessment studies and/or deferral/partial waiver/full waiver of pediatric studies (or request for deferral/partial waiver/full waiver of pediatric studies) included? Submitted in original NDA. YES NO X
- If the submission contains a request for deferral, partial waiver, or full waiver of studies, does the application contain the certification required under FD&C Act sections 505B(a)(3)(B) and (4)(A) and (B)? Submitted in original NDA. YES NO X
- Is this submission a partial or complete response to a pediatric Written Request? YES NO X

If yes, contact PMHT in the OND-IO

- Financial Disclosure forms included with authorized signature? YES X NO
(Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an agent.)
NOTE: Financial disclosure is required for bioequivalence studies that are the basis for approval.
- Field Copy Certification (that it is a true copy of the CMC technical section) YES NO X
- PDUFA and Action Goal dates correct in tracking system? YES X NO
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.
- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered.
- List referenced IND numbers: 58,460, 32,292
- Are the trade, established/proper, and applicant names correct in COMIS? YES X NO
If no, have the Document Room make the corrections.
- End-of-Phase 2 Meeting(s)? Date(s) _____ NO X
If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? Date(s) _____ NO X
If yes, distribute minutes before filing meeting.
- Any SPA agreements? Date(s) 8-31-05; 11-10-05 NO
If yes, distribute letter and/or relevant minutes before filing meeting.

Project Management

- If Rx, was electronic Content of Labeling submitted in SPL format? YES X NO
If no, request in 74-day letter.
- If Rx, for all new NDAs/efficacy supplements submitted on or after 6/30/06:
Was the PI submitted in PLR format? YES NO
If no, explain. Was a waiver or deferral requested before the application was received or in the submission? If before, what is the status of the request: *PLR is not required since this is a resubmission following an approvable letter.*
- If Rx, all labeling (PI, PPI, MedGuide, carton and immediate container labels) has been consulted to DDMAC? YES X NO
- If Rx, trade name (and all labeling) consulted to OSE/DMETS? YES X NO
 - If Rx, MedGuide and/or PPI (plus PI) consulted to ODE/DSRCS? N/A YES NO
- Risk Management Plan consulted to OSE/IO? N/A X YES NO
- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling submitted? NA X YES NO

If Rx-to-OTC Switch or OTC application: N/A

- Proprietary name, all OTC labeling/packaging, and current approved PI consulted to OSE/DMETS? YES NO
- If the application was received by a clinical review division, has DNPCE been notified of the OTC switch application? Or, if received by DNPCE, has the clinical review division been notified? YES NO

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? N/A YES NO

Chemistry (Note: The environmental assessment was submitted in the original NDA.)

- Did applicant request categorical exclusion for environmental assessment? YES NO X
If no, did applicant submit a complete environmental assessment? YES NO X
If EA submitted, consulted to EA officer, OPS? YES NO

- Establishment Evaluation Request (EER) submitted to DMPQ? YES X NO
- If a parenteral product, consulted to Microbiology Team? N/A YES NO

ATTACHMENT

MEMO OF FILING MEETING

DATE: 7-25-06

NDA #: 21-398

DRUG NAMES: COMBIGAN™ (brimonidine tartrate/timolol maleate ophthalmic solution)

APPLICANT: Allergan, Inc.

BACKGROUND: Allergan, Inc. (Allergan), originally submitted this NDA on September 17, 2001. The Agency issued an approvable letter on June 5, 2002. Allergan submitted a complete response to that approvable letter on September 13, 2004. The Agency issued a second approvable letter on March 15, 2005. This submission is a complete response to the March 14, 2005, approvable letter.

ATTENDEES: Alison Rodgers, Chris Khedouri, Thamban Valappil, Arzu Selen, Zhou Cehn, Terry Peters, Lin Qi, William Boyd, Wiley Chambers

ASSIGNED REVIEWERS (including those not present at filing meeting) :

Discipline/Organization

Reviewer

Medical:	William Boyd
Secondary Medical:	N/A
Statistical:	Chris Khedouri
Pharmacology:	Zhou Chen
Statistical Pharmacology:	N/A
Chemistry:	Lin Qi
Environmental Assessment (if needed):	
Biopharmaceutical:	N/A
Microbiology, sterility:	Bryan Riley
Microbiology, clinical (for antimicrobial products only):	N/A
DSI:	
OPS:	
Regulatory Project Management:	Alison Rodgers
Other Consults:	
DMETS	
DDMAC	Sheila Ryan

Per reviewers, are all parts in English or English translation? YES X NO

If no, explain:

CLINICAL FILE X REFUSE TO FILE

- Clinical site audit(s) needed? YES NO X
If no, explain:
- Advisory Committee Meeting needed? YES, date if known _____ NO X

- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?

	N/A	X	YES	<input type="checkbox"/>	NO	<input type="checkbox"/>
CLINICAL MICROBIOLOGY	N/A	X	FILE	<input type="checkbox"/>	REFUSE TO FILE	<input type="checkbox"/>
STATISTICS	N/A	<input type="checkbox"/>	FILE	X	REFUSE TO FILE	<input type="checkbox"/>
BIOPHARMACEUTICS FILE	N/A			<input type="checkbox"/>	REFUSE TO FILE	<input type="checkbox"/>

- Biopharm. study site audits(s) needed?
YES NO

PHARMACOLOGY/TOX	N/A	<input type="checkbox"/>	FILE	X	REFUSE TO FILE	<input type="checkbox"/>
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- GLP audit needed? YES NO

CHEMISTRY			FILE	X	REFUSE TO FILE	<input type="checkbox"/>
-----------	--	--	------	---	----------------	--------------------------

- Establishment(s) ready for inspection? YES NO
- Sterile product? YES X NO
- If yes, was microbiology consulted for validation of sterilization? YES X NO

ELECTRONIC SUBMISSION:
Any comments:

REGULATORY CONCLUSIONS/DEFICIENCIES:
(Refer to 21 CFR 314.101(d) for filing requirements.)

- The application is unsuitable for filing. Explain why:
- X The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.
- X No filing issues have been identified.
- Filing issues to be communicated by Day 74. List (optional):

ACTION ITEMS:

1. Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into COMIS.
2. If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.
3. If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.

4. If filed, complete the Pediatric Page at this time. (If paper version, enter into DFS.)
5. Convey document filing issues/no filing issues to applicant by Day 74.

Alison Rodgers
Regulatory Project Manager

Appendix A to NDA Regulatory Filing Review

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the

original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),

- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's Office of Regulatory Policy representative.

**Appendix B to NDA Regulatory Filing Review
Questions for 505(b)(2) Applications**

1. Does the application reference a listed drug (approved drug)? * YES X NO
* **PLEASE SEE EXPLANATION ATTACHED**

If "No," skip to question 3.

2. Name of listed drug(s) referenced by the applicant (if any) and NDA/ANDA #(s): Timolol Maleate *

3. Is this application for a drug that is an "old" antibiotic (as described in the draft guidance implementing the 1997 FDAMA provisions? (Certain antibiotics are not entitled to Hatch-Waxman patent listing and exclusivity benefits.)

YES NO X

If "Yes," skip to question 7.

4. Is this application for a recombinant or biologically-derived product?

YES NO X

If "Yes" contact your ODE's Office of Regulatory Policy representative.

5. The purpose of the questions below (questions 5 to 6) is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

- (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved?

YES NO X

(Pharmaceutical equivalents are drug products in identical dosage forms that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; and (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c))

If "No," to (a) skip to question 6. Otherwise, answer part (b and (c)).

- (b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES NO

- (c) Is the approved pharmaceutical equivalent(s) cited as the listed drug(s)?

YES NO

If "Yes," (c), list the pharmaceutical equivalent(s) and proceed to question 6.

If "No," to (c) list the pharmaceutical equivalent and contact your ODE's Office of Regulatory Policy representative.

Pharmaceutical equivalent(s):

6. (a) Is there a pharmaceutical alternative(s) already approved? YES NO X

(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

If "No," to (a) skip to question 7. Otherwise, answer part (b and (c)).

- (b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval? YES NO

- (c) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)? YES NO

If "Yes," to (c), proceed to question 7.

NOTE: *If there is more than one pharmaceutical alternative approved, consult your ODE's Office of Regulatory Policy representative to determine if the appropriate pharmaceutical alternatives are referenced.*

If "No," to (c), list the pharmaceutical alternative(s) and contact your ODE's Office of Regulatory Policy representative. Proceed to question 7.

Pharmaceutical alternative(s):

7. (a) Does the application rely on published literature necessary to support the proposed approval of the drug product (i.e. is the published literature necessary for the approval)? YES NO X

If "No," skip to question 8. Otherwise, answer part (b).

(b) Does any of the published literature cited reference a specific (e.g. brand name) product? Note that if yes, the applicant will be required to submit patent certification for the product, see question 12.

8. Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution"). This application provides for a combination product.
9. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA may refuse-to-file such NDAs (see 21 CFR 314.101(d)(9)).) YES NO X
10. Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application may be refused for filing under 21 CFR 314.101(d)(9)). YES NO X

11. Is the application for a duplicate of a listed drug whose only difference is that the rate at which the product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the RLD (see 21 CFR 314.54(b)(2))? If yes, the application may be refused for filing under 21 CFR 314.101(d)(9). YES NO
12. Are there certifications for each of the patents listed in the Orange Book for the listed drug(s) referenced by the applicant (see question #2)? (This is different from the patent declaration submitted on form FDA 3542 and 3542a.) YES NO

13. Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

- Not applicable (e.g., solely based on published literature. See question # 7)
- 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
Patent number(s):
- X 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)
Patent number(s):
- 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)
Patent number(s):
- 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification)
Patent number(s):

NOTE: IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must **subsequently** submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]. The applicant must also submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]. OND will contact you to verify that this documentation was received.

- 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).
Patent number(s):
- Written statement from patent owner that it consents to an immediate effective date upon approval of the application.
Patent number(s):
- 21 CFR 314.50(i)(1)(ii): No relevant patents.
- 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)
Patent number(s):

14. Did the applicant:

- Identify which parts of the application rely on the finding of safety and effectiveness for a listed drug or published literature describing a listed drug or both? For example, pharm/tox section of application relies on finding of preclinical safety for a listed drug.

YES NO

If "Yes," what is the listed drug product(s) and which sections of the 505(b)(2) application rely on the finding of safety and effectiveness or on published literature about that listed drug

Was this listed drug product(s) referenced by the applicant? (see question # 2)

YES NO

- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug(s)?

N/A YES NO

15. (a) Is there unexpired exclusivity on this listed drug (for example, 5 year, 3 year, orphan or pediatric exclusivity)? Note: this information is available in the Orange Book.

YES NO

If "Yes," please list:

Application No.	Product No.	Exclusivity Code	Exclusivity Expiration

NDA 21-398

Drug: Combigan (brimonidine tartrate/timolol maleate)

Sponsor: Allergan

Allergan submitted NDA 21-398 on September 18, 2001, as a 505 (b)(1) application. It received an approvable (AE) action on June 5, 2002. Allergan submitted a complete response to the AE on June 5, 2002. [During this review cycle it was noted that the submission should be a 505(b)(2) application as it relied on the Agency's previous findings of safety and efficacy for timolol maleate (NDAs 18-086 and 19-463, both owned by Merck)]. Again, the application received an AE on March 15, 2005. One of the deficiencies cited was the need for patent certification for the primary source data for timolol maleate.

NDA's 18-086 and 19-463 are owned by Merck and are the reference listed drugs in the Orange Book. Allergan provided a paragraph 2 certification as the Merck patents have expired. Allergan owns NDA 20-613 for .2% brimonidine tartrate although the product has been discontinued.

Allergan submitted a complete response to the second AE on July 29, 2006. The application was submitted as a 505(b)(1). The sponsor has been requested to revise form 356h to reflect that the application is a 505(b)(2). The application included a paragraph 2 certification for timolol maleate (NDAs 18-086 and 19-463).

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/s/

Alison Rodgers
10/3/2006 11:32:08 AM
CSO

Alison Rodgers
10/3/2006 11:36:43 AM
CSO

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: August 18, 2006

TO: File

FROM: Alison Rodgers

SUBJECT: **NDA 21-398 Resubmission June 29, 2006**
NDA 21-398, COMBIGAN (brimonidine tartrate/timolol maleate
ophthalmic solution)

The June 29, 2006 resubmission of NDA 21-398 is acceptable from a project management standpoint.

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

/s/

Alison Rodgers
8/18/2006 09:45:28 AM
CSO

Alison Rodgers
8/18/2006 10:08:12 AM
CSO



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-398

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

Dear Dr. Gryziewicz:

We acknowledge receipt on June 30, 2006, of your June 29, 2006 resubmission to your new drug application for COMBIGAN™ (brimonidine tartrate/timolol maleate ophthalmic solution) 0.2%/0.5%.

We consider this a complete, class 2 response to our March 14, 2005, action letter. Therefore, the user fee goal date is December 31, 2006.

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

Sincerely,

{See appended electronic signature page}

Maureen P. Dillon-Parker
Chief, Project Management Staff
Division of Anti-Infective and
Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

Maureen Dillon-Parker

8/2/2006 05:09:49 PM

NDA 21-398; Acknowledgement of resubmission



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:

We acknowledge receipt on September 14, 2004, of your September 13, 2004, submission to your new drug application for Combigan (brimonidine tartrate-timolol maleate ophthalmic solution) 0.2%/0.5%.

We consider this a complete, class 2 response to our June 5, 2002, action letter. Therefore, the user fee goal date is March 14, 2005.

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

Sincerely,

{See appended electronic signature page}

Carmen DeBellas, R.Ph.
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

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/s/

Michael Puglisi
9/29/04 04:14:17 PM
for Carmen DeBellas

2. RESULTS (by site):

Name	City	State	IN	Assigned	Action Date	Reviewer	Class
Lozier	San Diego	CA	DA	1/9/02	4/25/02	CAC	VAI
Evans	San Antonio	TX	DA	1/9/02	4/25/02	GRH	VAI
Wirta	Newport Beach	CA	DA	1/9/02	3/11/02	CAC	VAI

Jeffrey R. Lozier, M.D. – Protocol 190342-012-01

This site enrolled a total of 39 subjects. Thirteen subject's files were reviewed in depth and the only finding was that one subject had been enrolled prior to receiving medical clearance for a history of cardiovascular disease. There was no indication of underreporting of adverse events. The data appear acceptable.

Richard M. Evans, M.D. – Protocol 190342-012-01

This site enrolled 35 subjects with 30 completing the study. Of the subject records reviewed in depth, minor findings such as 3 subjects receiving the SITA-Fast field test instead of the SITA Standard Test and record keeping deficiencies were found. There was no indication of underreporting of adverse events. The data appear acceptable.

David L. Wirta, M.D. – Protocol 190342-012-01

This site enrolled 42 subjects. Fifteen subject's files were reviewed in detail. There was only one finding regarding 3 subjects who were not reconsented for the pharmacokinetic arm of the trial. There was no indication of underreporting of adverse events. The data appear acceptable.

3. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

No major deficiencies were noted in the three sites inspected that could compromise the integrity of the data. Thus, the data reviewed is acceptable. No subsequent actions or follow up inspections should be undertaken.

CC:

HFD-45/Reading File

HFD-47/El-Hage/Shibuya/Currier

HFD-47/rf/cf

O:\RS\NDA21-377\ClinInspectSumm21-398

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

/s/

Michele Balser

5/10/02 08:56:30 AM

TECHNICAL

Original was signed by Dr. ElHage on 5/2/02.

MEETING MINUTES

MEETING DATE: 5/30/01 TIME: 2:00pm LOCATION: CORP. S200A

IND # 58,460

Meeting Request Submission Date – 2/27/01

Date Sponsor Requested – 5/30/01

Meeting Packages Submitted – 4/30/01

DRUG: Brimonidine-Timolol Ophthalmic Solution

SPONSOR: Allergan, Inc.

TYPE OF MEETING: Pre-NDA

FDA PARTICIPANTS:

Wiley A. Chambers/ Deputy Division Director

Jonca Bull/ ODE V Deputy Director

William Boyd/ Medical Officer

Joanne Holmes/ Clinical Reviewer

Jennifer Harris/ Medical Officer

Lucious Lim/ Medical Officer

Zhou Chen/ Pharmacologist

Laura Lu/ Statistics Reviewer

Lori Gorski/ Project Manager

Raphael Rodriguez/ Project Manager

Linda Ng/ Chemistry Team Leader

Libaniel Rodriguez/ Chemistry Reviewer

Stan Lin/ Statistics Team Leader

Michael Puglisi/ Project Manager

INDUSTRY PARTICIPANTS:

Melvin Olson/ Biostatistician

Cheryl Larson/ Clinical Research

Scott Whitcup/ Clinical Research

Amy Batoosingh/ Clinical Research

Lawrence Lima/ Chemistry & Manufacturing

Peter Kresel/ Senior V.P., Regulatory Affairs

Lewis Gryziewicz/ Director, Regulatory Affairs

Christine Brissey/ Regulatory Affairs

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Questions to the Agency

OVERALL

1. Allergan plans to submit the NDA in electronic format in compliance with the FDA Guidance for Industry “Providing Regulatory Submissions in Electronic Format - NDAs”. Does FDA want a paper copy of any or all parts of the NDA?

Agency Response: *Yes. The Agency would like but does not require a complete paper archival copy of the NDA submission.*

CHEMISTRY

2. Brimonidine Tartrate 0.2% / Timolol 0.5% Ophthalmic Solution will be manufactured using Active Pharmaceutical Ingredients from the approved suppliers in NDA 20-613 ALPHAGAN® (brimonidine tartrate ophthalmic solution) 0.2%, ANDA 74-746, Timolol Maleate Ophthalmic Solution 0.25% and ANDA 74-747, Timolol Maleate Ophthalmic Solution 0.5%. We propose to cross-reference these applications for the API and that no such information is required for the upcoming Brimonidine Tartrate 0.2% / Timolol 0.5% Ophthalmic Solution NDA submission. Please comment.

Agency Response: *This proposal is acceptable. LOA to cross-reference these NDAs or DMFs should be submitted. CFN address and contact persons should be submitted for all sites relating to drug substance and drug product.*

3. Allergan understands that [REDACTED] is currently under review of the FDA’s compliance division. Allergan performed stability of Brimonidine Tartrate 0.2% / Timolol 0.5% Ophthalmic Solution using two lots of brimonidine tartrate manufactured by [REDACTED] and one by [REDACTED]. Allergan proposes to study four batches of Brimonidine Tartrate 0.2% / Timolol 0.5% Ophthalmic Solution for commercial stability, using three lots of brimonidine tartrate from [REDACTED]. Please comment.

Agency Response: *This proposal is acceptable.*

4. Allergan analyzed for container/closure extractables in Brimonidine Tartrate 0.2% / Timolol 0.5% Ophthalmic Solution using four methods: [REDACTED]

[REDACTED]

Allergan commits to a specification for

unspecified/unidentified related substances of NMT [redacted] of AGN 190342-LF label claim for the ongoing use of [redacted]. Allergan proposes that no extractables specification is required for this product. Please comment.

***Agency Response:** The proposal to set acceptance criteria of NMT [redacted], of label claim of AGN 190342-LF for unspecified/unidentified related substances and extractables is acceptable. Establishment of acceptance criteria will be discussed based on the data submitted in the NDA application.*

NONCLINICAL

5. As agreed to during the February 8, 1999 end-of-phase 2 meeting, no pharmacology studies were conducted with Brimonidine Tartrate 0.2% / Timolol 0.5% Ophthalmic Solution. No other pharmacology data will be presented. Allergan proposes to include a short introduction justifying the combination of these two ingredients in the Pharmacology sections of the NDA. Please comment.

***Agency Response:** Acceptable.*

6. During the February 8, 1999 end-of-phase 2 meeting it was agreed that no additional nonclinical ADME studies for the combination product are required. However, limited but relevant pharmacokinetic studies were performed to support formulation screening studies and compare ocular distribution of single and combination drug product. Toxicokinetics data were provided for the 6-month ocular Toxicology study in rabbits. The Nonclinical ADME section of the NDA will contain a discussion of these studies only. Please comment.

***Agency Response:** Acceptable.*

7. During the February 8, 1999 end-of-phase 2 meeting, it was agreed that since the ingredients in the formulation have not changed, no additional toxicology studies were needed. Since the combination is intended for global registration, a 6-month ocular study in rabbits was conducted to evaluate the safety of Brimonidine Tartrate 0.2% / Timolol 0.5% Ophthalmic Solution (Allergan study report TX99070). A 1-month ocular study in rabbits was conducted to evaluate the safety of impurity [redacted] and impurity [redacted] (Allergan study report TX01001). The two study reports, tabular and written summaries will be provided in the NDA. The Toxicology section of the NDA will consist of an overall summary describing the significant findings in animals for the single components as well as the combination. The previously submitted Brimonidine Tartrate and Brimonidine Purite, NDAs 20-613 and 21-262, respectively, will be cross-referenced. Study reports, tabular and written summaries will not be provided for studies submitted in support of the prior NDAs. Please comment.

***Agency Response:** Acceptable.*

HUMAN PHARMACOKINETICS

8. The Clinical Pharmacokinetics section of the NDA will include a study report for one clinical pharmacokinetic study evaluating systemic exposure of Brimonidine Tartrate 0.2% / Timolol 0.5% Ophthalmic Solution as compared to that of Brimonidine Tartrate 0.2% Ophthalmic Solution and Timolol 0.5% Ophthalmic Solution.). In addition, systemic drug exposure of brimonidine and timolol are evaluated in two Phase 3 studies. Please comment.

Agency Response: The proposed studies for the Human Pharmacokinetics section of the NDA is acceptable. This section should also include the assay validation and assay quality control reports for the brimonidine tartrate and timolol.

MICROBIOLOGY

- 9.

Agency Response: Acceptable.

CLINICAL and STATISTICAL

10. The Statistical Analysis plan submitted to IND 58,460 on October 16, 2000 proposed including Patient Data Listings under Appendix 16.2 of the phase 3 study reports as per ICH E3. Allergan proposed to not include Individual Patient Data Listings (US Archival Listings) under Appendix 16.4 as per ICH E3 in the final study reports or in Section 11, Case Report Tabulations, of the NDA. In place of Appendix 16.4, Allergan will provide FDA with electronic SAS Transport Files for all datasets in Section 11 of the NDA, formatted in compliance with the FDA Guidance "Providing Regulatory Submissions in Electronic Format – NDAs". Please comment.

Agency Response: Acceptable.

11. The analysis plan for protocols 190342-012T and -013T were revised and issued before the database lock of the first study (-012T) with minor modifications to the original analysis plan reviewed by the Agency. We have included the modified analysis plan, with a summary of the changes as a cover sheet, for review. Please confirm acceptability.

Agency Response: Acceptable.

with glaucoma or ocular hypertension and that the Combination had a safety profile that was superior to Brimonidine and at least as good as Timolol. The analyses presented provide sufficient information for evaluation of the approvability of this product according to the agreed upon criteria. Please comment.

***Agency Response:** The Agency will apply the criteria set forth in 21 CFR §300.50 for fixed combination products. The Agency expects to see replication of study results in a minimum of two separate independent Phase 3 controlled trials. The Phase 3 trials should demonstrate superiority of the fixed combination over each individual components by a clinically significant amount. Differences of 2 mmHg are commonly seen in clinical trials without a change in therapy.*

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/s/

Wiley Chambers
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