CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-764

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Alcon, Inc.
PATENT CERTIFICATION

Paragraph IV Certification

Pursuant to section 505(b)(2)(A) of the Federal Food, Drug and Cosmetic Act ("the Act") Alcon, Inc. ("Alcon") hereby certifies that, in its opinion and to the best of its knowledge, United States Patent Nos. 5,424,078; 6,562,873; 6,627,210; 6,641,834; and 6,673,337 are invalid and/or will not be infringed by the manufacture, use, offer for sale or sale of Alcon's Brimonidine Tartrate Ophthalmic Solution, 0.15%, for which this application is submitted.

Pursuant to the requirements of 21 CFR 314.52(a) and 21 CFR 314.52(c), Alcon will provide notice of the submission of this application and a detailed statement of the factual and legal basis for Alcon's opinion that U.S. Patent Nos. 5,424,078; 6,562,873; 6,627,210; 6,641,834; and 6,673,337 are invalid and/or will not be infringed to Allergan, Inc., 2525 Dupont Drive, Irvine, CA 92612, as the holder of the approved application under section 505(b) of the Act, and Allergan, Inc, and Allergan Sales, Inc., both of 2525 Dupont Drive, Irvine, CA 92612, as the patent owners of record.

On behalf of Alcon, Inc.

April 22, 2004
Date

Patrick M. Ryan

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EXCLUSIVITY SUMMARY FOR NDA # **21-764** SUPPL #_____

Trade Name N/A Generic Name **brimonidine tartrate ophthalmic solution, 0.15%**

Applicant Name **Alcon, Inc. / Alcon Research, Ltd.** **HFD-550**

Approval Date If Known **February 25, 2005**

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 question about the submission.

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

YES /**XX**/ 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 /**XX**/

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.

The study was designed and performed as a bioavailability Study and bioequivalence study with a clinical endpoint.

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 /_ **XX**__/ NO /_ _/

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

___**3 years**_____

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

YES /_ **XX**__/ NO /_ /

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

_____**Yes**_____

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 /**XX**/

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 /_**XX**_ / NO /___/

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

NDA# **21-262**

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 /__**XX**__ /

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

NDA#

NDA#

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 NDA'S 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 /_**XX**_/

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:

_____

_____

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 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 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"):

_____ _____

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 # _____ 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 identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ ! NO /___/ Explain _____

_____ ! _____

_____ ! _____

Investigation #2

YES /___/ Explain _____ ! NO /___/ Explain _____

_____ ! _____

_____ ! _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not

be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

_____

Signature_____ Date _____
Raphael R. Rodriguez
RPM

Signature_____ Date 2/25/05
Rhea Lloyd, M.D.
Clinical Reviewer

Signature_____ Date _____
Wiley A. Chambers, M.D.
Deputy Director

Form OGD-011347 Revised 05/10/2004

cc:
Archival NDA 21-764
HFD-550 /Division File
HFD-550 /RPM / RodriguezR
HFD-610/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

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3.A.10. STATEMENTS OF CLAIMED EXCLUSIVITY AND ASSOCIATED CERTIFICATIONS

The applicant hereby requests a three-year period of exclusivity.

Pursuant to 21CFR 314.50(j) and 21CFR314.108(b)(4), I hereby certify that:

- To the best of my knowledge each of the clinical investigations included in the application meets the definition of "new clinical investigation".
- The new clinical investigations are essential to the approval of the application.
- Alcon, Inc. was named as the sponsor on the form FDA 1571 for an investigation new drug application (IND #64,330) under which the clinical investigations that are essential to the approval of this application were conducted.

Michael E Pfleger

Michael Pfleger
Senior Director, Regulatory Affairs
Tel. 817-551-4877

4/12/04
Date

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PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA # : 21-764 **Supplement Type (e.g. SE5):** _____ **Supplement Number:**

Stamp Date: April 28, 2004 **Action Date:** February 28, 2005

HFD 550 **Trade and generic names/dosage form:** Brimonidine Tartrate Ophthalmic Solution, 0.15%

Applicant: Alcon, Inc. / Alcon Research, Ltd. **Therapeutic Class:** 404110, Alpha Adrenergic Agonist

Indication(s) previously approved:

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: lowering of intraocular hypertension in open angle glaucoma or ocular hypertension

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

XX 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:

XX 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:

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:

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:

Min _____ **kg**_____ **mo.**_____ **yr.** 2 **Tanner Stage**_____
Max_____ **kg**_____ **mo.**_____ **yr.** 7 **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.

This page was completed by:

{See appended electronic signature page}

Raphael Rodriguez_____
Regulatory Project Manager

Rhea Lloyd, M.D._____
Clinical Reviewer

cc: **NDA 21-764**
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 12-22-03)

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

/s/

Wiley Chambers
3/3/05 03:42:13 PM

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3.A.8. WAIVER REQUESTS

3.A.8.1 Pediatric Waiver Request

Pursuant to 21 CFR§314.55(c)(3), the applicant requests a waiver of information regarding the use of Brimonidine Tartrate Ophthalmic Solution, 0.15% in pediatric patients.
This waiver is requested for the following reasons:
1) The safety and effectiveness of brimonidine tartrate ophthalmic solution, 0.2% has been studied in pediatric glaucoma patients between 2 and 7 years of age (approved labeling for ALPHAGAN®, ALPHAGAN® P, and Brimonidine Tartrate Ophthalmic Solution, 0.2%).
2) Brimonidine tartrate is not recommended for use in patients under the age of 2 years.

3.A.8.2 Request for Waiver of Evidence of In vivo Bioavailability or Bioequivalence

Pursuant to 21CFR§320.22(b)(1) the applicant requests a waiver from the requirements for submission of *in vivo* bioavailability or bioequivalence data. The drug product is an ophthalmic solution; and contains the same active ingredients in the same concentration as are the subject of approved full new drug applications.

Brimonidine Tartrate Ophthalmic Solution, 0.15% contains brimonidine tartrate at a concentration of 0.15% as the active ingredient. Brimonidine tartrate at a concentration of 0.15% (equivalent to 1.5 mg/mL) is the active ingredient in ALPHAGAN®P [NDA 21-262].

3.A.3. DEBARMENT CERTIFICATION

Alcon, Inc. and its affiliate companies [Alcon Research, Ltd., Alcon Laboratories, Inc., and Alcon Manufacturing, Ltd.] hereby certify 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.

Michael Pfleger
Senior Director, Regulatory Affairs
Tel. 817-551-4877

4/12/04
Date

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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: February 28, 2006.

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		
	All investigators on the attached list participating	
	in Brimonidine Tartrate 0.15% Ophthalmic Solution	
	Study C-03-01	

☐ (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	TITLE
George P. Morey	Vice President, Controller
FIRM / ORGANIZATION: Alcon Research Ltd.	
SIGNATURE: George P Morey	DATE: 2 April 2004

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

Created by: PSC Media Arts Branch (301) 443-1090 EF

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

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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

All investigators on the attached list participating

in Study C-02-49 Brimonidine Tartrate 0.15% Ophthalmic Solution

☐ (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	TITLE
George P. Morey	Vice President, Controller
FIRM / ORGANIZATION: Alcon Research Ltd.	
SIGNATURE: George P Morey	DATE: 2 April 2004

Paperwork Reduction Act Statement

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Food and Drug Administration
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Rockville, MD 20857

Created by: PSC Media Arts Branch (301) 443-1090 EF

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Food and Drug Administration

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Expiration Date: February 28, 2006

DISCLOSURE: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

The following information concerning [redacted], who
Name of clinical investigator

ticipated as a clinical investigator in the submitted study Brimonidine Tartrate 0.15% Ophthalmic Solution
Name of clinical study

for the period January 2, 2003 to February 26, 2004, is submitted in accordance with 21 CFR

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	TITLE
George P. Morey	Vice President, Controller
FIRM / ORGANIZATION: Alcon Research, Ltd.	
SIGNATURE: George P Morey	DATE: 26 April 2004

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 4 hours 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:

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Food and Drug Administration
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Rockville, MD 20857

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Form Approved: OMB No. 0910-0396
Expiration Date: February 28, 2006

DISCLOSURE: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

The following information concerning [redacted], who
Name of clinical investigator

participated as a clinical investigator in the submitted study Brimonidine Tartrate 0.15% Ophthalmic Solution
Name of clinical study

for the period January 2, 2003 to February 26, 2004, is submitted in accordance with 21 CFR 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	TITLE
George P. Morey	Vice President, Controller
FIRM / ORGANIZATION: Alcon Research, Ltd.	
SIGNATURE: George P Morey	DATE: 2 April 2004

Paperwork Reduction Act Statement

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Expiration Date: February 28, 2006

DISCLOSURE: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

The following information concerning [redacted], who
Name of clinical investigator

participated as a clinical investigator in the submitted study Brimonidine Tartrate 0.15% Ophthalmic Solution
Name of

[redacted] for the period January 2, 2003 to February 26, 2004, is submitted in accordance with 21 CFR
clinical study

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;

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FIRM / ORGANIZATION: Alcon Research, Ltd.	
SIGNATURE: George P Morey	DATE: 2 April 2004

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Form Approved: OMB No. 0910-0396
Expiration Date: February 28, 2006

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TO BE COMPLETED BY APPLICANT

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Name of clinical investigator

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Name of clinical study

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3.A.6.3. COMPLETED CERTIFICATION AND DISCLOSURE FORMS

Completed certification (form FDA-3454) and disclosure (form FDA-3455) forms for clinical studies of Brimonidine Tartrate Ophthalmic Solution, 0.15% are included in this submission as per Table 3.A.6.3-1.

Table 3.A.6.3-1

Financial Certification and Disclosure Forms Included in this Submission

Clinical Protocol	**Form**	**Investigator(s)**
C-03-01	Form FDA-3454 (certification)	All investigators
C-02-49	Form FDA-3454 (certification)	[redacted]
C-02-49	Form FDA-3455 (disclosure)	[redacted]

Table 3.A.6.3-1 (continued)

Financial Certification and Disclosure Forms Included in this Submission

C-02-49	Form FDA-3455 (disclosure)	[redacted]

Appears This Way
On Original

3.A.6. FINANCIAL DISCLOSURE

3.A.6.1. CERTIFICATION AND DISCLOSURE STATEMENTS

Pursuant to 21 CFR§314.50(k), §312.53(c)(4), and §54.4, the following is certification and disclosure information for the covered clinical studies submitted in this application.

The covered clinical studies include: C-02-49 and C-03-01.

The applicant has determined that there were no financial interests or arrangements to disclose from the investigator that participated in C-03-01. However, there are financial interests or arrangements to disclose from sixteen investigators, presented in Table 3.A.6.1-1, that participated in C-02-49.

Table 3.A.6.1-1

Investigators with Financial Interests or Arrangements

Covered Clinical Study	Investigators with Financial Interests or Arrangements to Disclose
C-02-49	⌜ ⌟

Completed Certification Forms (FDA form-3454) and Disclosure Forms (FDA form-3455) signed by the applicant's Financial Officer are provided in Module 1, Section 3.A.6.3. The claims in the signed form FDA-3454 and form FDA-3455 have been verified by documentation obtained from the investigators. The list of investigators with disclosure for this covered clinical study, C-02-49, is provided in Module 1, Section 3.A.6.2.

Description of Financial Interests and Arrangements by Investigator

Reporting Period: January 02, 2003 to February 26, 2004

(sub-investigator: [redacted]

Description	
Consulting	$58,416.00
Travel Expenses	$2,659.42
Total	$61,075.42

(sub-investigators: [redacted]

Description	
Research Fund - [redacted]	$35,500.00
Total	$35,500.00

(sub-investigator: [redacted]

Description	
Consultant – [redacted]	$36,000.00
Expense Reimbursement – [redacted]	$3022.28
Honoraria – [redacted]	$500.00
Total	$39,522.28

(sub-investigator: [redacted]

Description	
Honoraria and Counsulting - [redacted]	$48,000.00
Honoraria – [redacted]	$2,000.00
Consulting – [redacted]	$46,750.00
Expense Reimbursement – [redacted]	$31,039.79
[redacted]	$67,500.00
[redacted]	$1,196.48
Total	$196,486.27

Description of Financial Interests and Arrangements by Investigator

Reporting Period: January 02, 2003 to February 26, 2004

(sub-investigators:

Description	Amount
Honoraria and Expenses –	$21,079.82
Honoraria and Expenses –	$2,000.00
Conventions and Expenses	$662.81
Consulting –	$2,500.00
Consulting –	$57,500.00
Honoraria and Meetings –	$46,001.42
Honoria and Meetings –	$14,600.17
Consulting -	$10,000.00
	$321.56
Consulting -	$176,085.00
Expenses -	$159.14
Total	$330,909.92

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Study-Related Factors For C-02-49 That Minimized Bias Regardless of Financial Interests and Arrangements:

- The study was double-masked such that neither the investigators (including their study staff) nor patients were aware of the treatment assignment.
- Assignment of treatment code was randomized.
- All study medications were solutions and were similar in appearance.
- Study medications were supplied in identical appearing opaque low density polyethylene bottles.
- The safety variables, which included visual acuity, fundus parameters, slit-lamp biomicroscopy, pulse and blood pressure measurements, and adverse events, were objective safety endpoints assessed by a masked observer.
- The treatment code was not broken at any time during any of the studies by either the investigator or the Sponsor.
- Frequent on-site monitoring was performed during the conduct of the studies to ensure compliance with protocol guidelines.

This submission is based on six-months of safety and efficacy data (primary efficacy based on three-months). However the study includes a six-month, planned, masked extension with a visit at Month 12. Currently, the investigators (including their study staff), patients, study monitors, and Alcon staff that are in contact with investigators remain masked as to the treatment assignment.

6 Page(s) Withheld

_____ Trade Secret / Confidential

X Draft Labeling

_____ Deliberative Process

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/s/

Wiley Chambers
2/28/05 12:01:38 AM

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VERSION (4/21/04)
INTERNAL/CONFIDENTIAL

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information			
NDA 21-764	Efficacy Supplement Type SE-	Supplement Number	
Drug: Brimonidine Tartrate Ophthalmic Solution, 0.15%		Applicant: Alcon, Inc. Alcon Research, Ltd.	
RPM: Raphael R. Rodriguez		HFD- 550	Phone # (301) 827-2519

Application Type: ( ) 505(b)(1) (X) 505(b)(2) (This can be determined by consulting page 1 of the NDA Regulatory Filing Review, if completed for this application. If not completed, or you otherwise have questions about whether an application is a 505(b)(1) or 505(b)(2) NDA, see Appendix A.) **If this is a 505(b)(2) application, please review and confirm the information previously provided in Appendix B to the NDA Regulatory Filing Review. Please update any information that is no longer correct.** ( ) Confirmed and/or corrected	Reference Listed Drug (NDA #, Drug name): NDA 21-622 Alphagan P (brimonidine tartrate ophthalmic solution) 0.15%

❖ Application Classifications:	
• Review priority	(X) Standard ( ) Priority
• Chem class (NDAs only)	5S
• Other (e.g., orphan, OTC)	
❖ User Fee Goal Dates	2/28/2005
❖ Special programs (indicate all that apply)	( ) None Subpart H ( ) 21 CFR 314.510 (accelerated approval) ( ) 21 CFR 314.520 (restricted distribution) ( ) Fast Track ( ) Rolling Review ( ) CMA Pilot 1 ( ) CMA Pilot 2
❖ User Fee Information	
• User Fee	(X) Paid UF ID number 4741
• User Fee waiver	( ) Small business ( ) Public health ( ) Barrier-to-Innovation (X) Other (specify) _
• User Fee exception	( ) Orphan designation ( ) No-fee 505(b)(2) (see NDA Regulatory Filing Review for instructions) (X) Other (specify)

	Paid in half User Fee. Submitted bioequivalence study. 10/27/2004 refund was granted.
❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	( ) Yes (X) No
• This application is on the AIP	( ) Yes (X) No
• Exception for review (Center Director's memo)	
• OC clearance for approval	
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification & certifications from foreign applicants are cosigned by US agent.	(X) Verified
❖ Patent	
• Information: Verify that form FDA-3542a was submitted.	(X) Verified
• Patent certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) ( ) I ( ) II ( ) III (X) IV 21 CFR 314.50(i)(1) ( ) (ii) ( ) (iii)
• [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be granted effective approval (but may be tentatively approved if it is otherwise ready for approval) until the date that the patent to which the certification pertains expires.	
• [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next box below (Exclusivity))*	( ) N/A (no paragraph IV certification) (X) Verified
• [505(b)(2) applications] For each paragraph IV certification, based on the questions below, determine whether a stay of approval is in effect due to patent infringement litigation. Answer the following questions for each paragraph IV certification:	
(1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? (Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))). *If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).*	(X) Yes ( ) No
(2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? *If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to next box below (Exclusivity).*	( ) Yes ( ) No

*If "**No**," continue with question (3).*

(3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant? (Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). The patent owner (or its representative) may, but is not required, to provide such notification (see 21 CFR 314.107(f)(2))).	**(X)** Yes ( ) No

*If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*

(4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?	( ) Yes **(X)** No

*If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to next box below (Exclusivity).*

*If "**No**," continue with question (5).*

(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). (The patent owner (or its representative) may, but is not required, to provide such notification (see 21 CFR 314.107(f)(2))). Note that the applicant has until the **later** of the following dates to provide the Division with this written notice: (a) the date marking the end of the 45-day period described in question (1), above, or (b) the date that the Division completes its review of the application (see 21 CFR 314.107(f)(2))).	**(X)** Yes ( ) No

*If "**No**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to next box below (Exclusivity).*

*If "**Yes**," a stay of approval may be in effect; answer the following questions.*

(6) (a) Was the patent subject to the paragraph IV certification submitted to FDA on or after August 18, 2003? (Note: This can be determined by checking with **[the Orange Book staff?]**.)	( ) Yes ( ) No

*If "**No**," skip to question 7. If "**Yes**," continue with part (b).*

(b) Was the patent also submitted to FDA before the date that this 505(b)(2) application was submitted as substantially complete? | **(X)** Yes | ( ) No

*If "**No**," there is no stay of approval based on the paragraph IV certification for this patent. If "**Yes**," continue with question (7).*

(7) (a) Have 30 months (or an alternate length of time ordered by the court, if any) passed from the date the patent owner received the applicant's notice of certification for the patent? | ( ) Yes | **(X)** No

(Note: In general, approval of a 505(b)(2) application cannot be made effective (although the application can be tentatively approved) for 30 months from the date that the patent owner receives the applicant's notice of certification if a patent infringement suit is timely initiated as described in question (5) above. However, the court may order that the 30-month period be shortened or lengthened under certain circumstances. If the court has ordered that the 30-month period be altered in a particular case, the applicant is required to submit a copy of the court order to the Division within 10 working days (see 21 CFR 314.107(e))).

*If "**No**," go to question (8). If "**Yes**," continue with part (b) of this question.*

(b) Before the expiration of the 30-month (or other) period described in part (a), above, did the district court hearing the patent infringement action decide whether the patent subject to the certification is invalid, unenforceable, or not infringed? (For purposes of this question, a district court decision would include a statement regarding the patent's invalidity, unenforceability, or noninfringement that is part of a settlement order or consent decree entered by the court, or a substantive determination by the court that there is no cause of action for patent invalidity or noninfringement.) | ( ) Yes | **(X)** No

(Note: To answer this question, you should check whether the Division has received a copy of a court order or judgment. The applicant is required to submit a copy of any such document to the Division within 10 working days (see 21 CFR 314.107(e))).

*If "**No**," there is no stay of approval based on the paragraph IV certification for this patent. Analyze the remaining paragraph IV certifications, if any, in this application. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).*

*If "**Yes**," continue with part (c) of this question.*

(c) Did the district court decide that the patent was invalid, unenforceable, or not infringed? | ( ) Yes | ( ) No

*If "**Yes**," there is no stay of approval based on the paragraph IV certification for this patent. Analyze the remaining paragraph IV certifications, if any, in this application. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).*

*If "**No**," (i.e., the district court decided that the patent was valid, enforceable, and infringed), continue with part (d) of this question.*

(d) If the district court's decision was appealed, has the appellate court issued a decision finding the patent invalid, unenforceable, or not infringed (including a statement to this effect that is part of a settlement order or consent decree entered by the appellate court, or a substantive determination by the court that there is no cause of action for patent invalidity or noninfringement)?

(Note: As mentioned above, the applicant is required to submit a copy of all court orders or judgments to the Division within 10 working days (see 21 CFR 314.107(e)); therefore, you can check to see whether a copy of an appellate court's order or judgment has been submitted.)

( ) Yes (X) No or N/A

*If "**Yes**," there is no stay of approval based on the paragraph IV certification for this patent. Analyze the remaining paragraph IV certifications, if any, in this application. If there are no other paragraph IV certifications, go to the next box below (Exclusivity).*

*If "**N/A**" (i.e., the district court decision was not appealed) or "**No**" (i.e., the appellate court has not yet issued a decision, or has decided that the patent was infringed), the application cannot be effectively approved until the date the patent expires. (If, before the date the patent expires, the appellate court decides that the patent is invalid, unenforceable, or not infringed, the application may be effectively approved as of the date of the appellate decision, if it otherwise qualifies for effective approval.) Analyze the remaining paragraph IV certifications, if any, in this application. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).*

(8) (a) Has the district court hearing the patent infringement action decided whether the patent subject to the certification is invalid, unenforceable, or not infringed? (For purposes of this question, a district court decision would include a statement regarding the patent's invalidity, unenforceability, or noninfringement that is part of a settlement order or consent decree entered by the court, or a substantive determination by the court that there is no cause of action for patent invalidity or noninfringement.)

(Note: To answer this question, you should check whether the Division has received a copy of a court order or judgment. The applicant is required to submit a copy of any such document to the Division within 10 working days (see 21 CFR 314.107(e))).

( ) Yes (X) No

*If "**No**," a stay of approval is currently in effect until the expiration of the time period described in (7)(a), above. The stay may be terminated or altered if the district court issues a decision regarding the patent's validity, enforceability, or infringement before the expiration of the time period described in (7)(a). If such a decision is issued before this time period expires, answer question (b) below.*

*If "**Yes**," continue with part (b) of this question.*

(b) Did the district court decide that the patent was invalid, unenforceable, or not infringed?

( ) Yes (X) No

*If "**Yes**," there is no stay of approval based on the paragraph IV certification for this patent. Analyze the remaining paragraph IV certifications, if any, in this application. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).*

*If "**No**," (i.e., the district court decided that the patent was valid, enforceable, and infringed), continue with part (c) of this question.* (c) If the district court's decision was appealed, has the appellate court issued a decision finding the patent invalid, unenforceable, or not infringed (including a statement to this effect that is part of a settlement order or consent decree entered by the appellate court, or a substantive determination by the court that there is no cause of action for patent invalidity or noninfringement)? (Note: As mentioned above, the applicant is required to submit a copy of all court orders or judgments to the Division within 10 working days (see 21 CFR 314.107(e)); therefore, you can check to see whether a copy of an appellate court's order or judgment has been submitted.) *If "**Yes**," there is no stay of approval based on the paragraph IV certification for this patent.* *If "**N/A**" (i.e., the district court decision was not appealed) or "**No**" (i.e., the appellate court has not yet issued a decision, or has decided that the patent was infringed), the application cannot be effectively approved until the date the patent expires. (If, before the date the patent expires, the appellate court decides that the patent is invalid, unenforceable, or not infringed, the application may be effectively approved as of the date of the appellate decision, if it otherwise qualifies for effective approval.) Analyze the remaining paragraph IV certifications, if any, in this application. If there are no other paragraph IV certifications, go to the next box below (Exclusivity).*	( ) Yes (**X**) No or N/A
❖ Exclusivity (approvals only)	
• Exclusivity summary • Is there remaining 3 year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)	N/A
• Is there an existing orphan drug exclusivity protection for the active moiety for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of sameness for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification!*	( ) Yes, Application #_____ (**X**) No
❖ Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)*	
General Information	
❖ Actions	
• Proposed action 2/28/2005	( ) AP (**X**) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	
• Status of advertising (approvals only)	(**X**) Materials requested in TA letter ( ) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	( ) Yes ( ) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	(**X**) None ( ) Press Release ( ) Talk Paper ( ) Dear Health Care Professional Letter

❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	2/24/2005
• Most recent applicant-proposed labeling	2/25/2005
• Original applicant-proposed labeling	4/27/2004
• Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	5/27/2004
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	2/24/2005
• Applicant proposed	4/27/2004
• Reviews	2/25/2005
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	
• Documentation of discussions and/or agreements relating to post-marketing commitments	
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	5/10, 11/21, 11/22/2004 & , 2/24/2005
❖ Memoranda and Telecons	
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	8/19/2003
• Pre-NDA meeting (indicate date)	none
• Pre-Approval Safety Conference (indicate date; approvals only)	N/A
• Other	
❖ Advisory Committee Meeting	
• Date of Meeting	N/A
• 48-hour alert	N/A
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	N/A
Summary Application Review	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)*	2/25/2005
Clinical Information	
❖ Clinical review(s) *(indicate date for each review)*	2/24/2005; 2/25/2005
❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	N/A
❖ Safety Update review(s) *(indicate date or location if incorporated in another review)*	2/25/2005
❖ Risk Management Plan review(s) *(indicate date/location if incorporated in another rev)*	N/A
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	ages 2-7 years
❖ Demographic Worksheet *(NME approvals only)*	N/A
❖ Statistical review(s) *(indicate date for each review)*	12/15/2004
❖ Biopharmaceutical review(s) *(indicate date for each review)*	2/7/2005
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	N/A
❖ Clinical Inspection Review Summary (DSI)	

• Clinical studies	10/27 & 11/18/2004
• Bioequivalence studies	2/7/2005
CMC Information	
❖ CMC review(s) *(indicate date for each review)*	2/3 & 2/24/2005
❖ Environmental Assessment	
• Categorical Exclusion *(indicate review date)*	2/3/2005
• Review & FONSI *(indicate date of review)*	N/A
• Review & Environmental Impact Statement *(indicate date of each review)*	N/A
❖ Microbiology (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	8/26/2004
❖ Facilities inspection (provide EER report)	Date completed: **(X)** Acceptable 2/3/2005 ( ) Withhold recommendation
❖ Methods validation	( ) Completed **(X)** Requested ( ) Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	1/26/2005
❖ Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	N/A
❖ CAC/ECAC report	N/A

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

/s/

Raphael Rodriguez
2/28/05 01:18:16 PM

ORIGINAL BL

2/25/05

Alcon
RESEARCH, Ltd.

6201 South Freeway
Fort Worth, Texas 76134-2099
(817) 293-0450

February 25, 2005

Dr. Wiley Chambers
Division of Analgesic, Anti-Inflammatory
and Ophthalmic Drug Products
CDER, HFD-550
Food and Drug Administration
Document Control Room
9201 Corporate Blvd.
Rockville, Maryland 20850

N-000(BL)
ORIG AMENDMENT

RE: **NDA 21-764 Brimonidine Tartrate Ophthalmic Solution, 0.15%**
Amendment to Application

Dear Dr. Chambers:

Please find enclosed modified labeling pursuant to our discussion with the Agency on February 24th and 25th, 2005.

There is no new safety information to be reported.

Please find enclosed two review copies and one archive copy of this amendment submission. A field copy has been sent to the Dallas office.

If you have any questions or comments concerning this amendment, please contact me via telephone at 817-551-4877 or via facsimile at 817-551-4630.

Sincerely,

Michael Pfleger
Senior Director Regulatory Affairs

Encl.

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On Original

ORIGINAL

BC

Alcon
RESEARCH, Ltd.

6201 South Freeway
Fort Worth, Texas 76134-2099
(817) 293-0450

February 22, 2005

Dr. Wiley Chambers
Division of Analgesic, Anti-Inflammatory
and Ophthalmic Drug Products
CDER, HFD-550
Food and Drug Administration
Document Control Room
9201 Corporate Blvd.
Rockville, Maryland 20850

N-000(BC)
ORIG AMENDMENT

RE: NDA 21-764 Brimonidine Tartrate Ophthalmic Solution, 0.15%
Amendment to Application

Dear Dr. Chambers:

Please find enclosed response to the FDA request of February 22, 2005 for a commitment to develop an ethylenediamine test method.

Please find enclosed two review copies and one archive copy of this amendment submission. A field copy has been sent to the Dallas office.

If you have any questions or comments concerning this amendment, please contact me via telephone at 817-551-4877 or via facsimile at 817-551-4630.

Sincerely,

Michael Pfleger
Senior Director Regulatory Affairs

Encl.

Appears This Way
On Original

ORIGINAL BC

2/25/05

Alcon
RESEARCH, Ltd.

6201 South Freeway
Fort Worth, Texas 76134-2099
(817) 293-0450

February 8, 2005

Dr. Wiley Chambers
Division of Analgesic, Anti-Inflammatory
and Ophthalmic Drug Products
CDER, HFD-550
Food and Drug Administration
Document Control Room
9201 Corporate Blvd.
Rockville, Maryland 20850

N-000(BC)
ORIG AMENDMENT

RE: NDA 21-764 Brimonidine Tartrate Ophthalmic Solution, 0.15%
Amendment to Application

Dear Dr. Chambers:

Please find enclosed response to the FDA request of January 28, 2005 to update the drug product specifications.

Please find enclosed two review copies and one archive copy of this amendment submission. A field copy has been sent to the Dallas office.

If you have any questions or comments concerning this amendment, please contact me via telephone at 817-551-4877 or via facsimile at 817-551-4630.

Sincerely,

Michael Pfleger
Senior Director Regulatory Affairs

Encl.

Appears This Way
On Original

ORIGINAL

Alcon

ALCON LABORATORIES, INC.
6201 South Freeway
Fort Worth, Texas 76134-2099
(817) 293-0450

February 3, 2005

Dr. Wiley Chambers
Division of Analgesic, Anti-Inflammatory
and Ophthalmic Drug Products
CDER, HFD-550
Food and Drug Administration
Document Control Room
9201 Corporate Blvd.
Rockville, Maryland 20850

ORIG AMENDMENT
N-000(BC)

RE: NDA 21-764 Brimonidine Tartrate Ophthalmic Solution, 0.15%
Amendment to Application

Dear Dr. Chambers:

Please find enclosed response to the FDA request of January 21, 2005 for an update on the stability data and other CMC issues.

Please find enclosed two review copies and one archive copy of this amendment submission. A field copy has been sent to the Dallas office.

If you have any questions or comments concerning this amendment, please contact me via telephone at 817-551-4877 or via facsimile at 817-551-4630.

Sincerely,

Appears This Way
On Original

Michael Pfleger
Senior Director Regulatory Affairs

Encl.

RECEIVED
FEB 14 2005
MEGA / CDER

RECEIVED
FEB 07 2005
OGD / CDER

DUPLICATE

Alcon
RESEARCH, Ltd.

6201 South Freeway
Fort Worth, Texas 76134-2099
(817) 293-0450

February 2, 2005

Dr. Wiley Chambers
Division of Analgesic, Anti-Inflammatory
and Ophthalmic Drug Products
CDER, HFD-550
Food and Drug Administration
Document Control Room
9201 Corporate Blvd.
Rockville, Maryland 20850

SUPPL NEW CORRESP
N-000(c)

RE: NDA 21-764 Brimonidine Tartrate Ophthalmic Solution, 0.15%
Amendment to Application

Dear Dr. Chambers:

Please find enclosed response to the FDA request of February 2, 2005 for information concerning the affected patents.

Please find enclosed two review copies and one archive copy of this amendment submission. A field copy has been sent to the Dallas office.

If you have any questions or comments concerning this amendment, please contact me via telephone at 817-551-4877 or via facsimile at 817-551-4630.

Sincerely

Michael Pfleger
Senior Director Regulatory Affairs

Encl.

RECEIVED
FEB 0 8 2005
MEGA / CDER

DUPLICATE

Alcon
RESEARCH, Ltd.

6201 South Freeway
Fort Worth, Texas 76134-2099
(817) 293-0450

February 1, 2005

ORIG AMENDMENT
N-000(BC)

Dr. Wiley Chambers
Division of Analgesic, Anti-Inflammatory
and Ophthalmic Drug Products
CDER, HFD-550
Food and Drug Administration
Document Control Room
9201 Corporate Blvd.
Rockville, Maryland 20850

RE: NDA 21-764 Brimonidine Tartrate Ophthalmic Solution, 0.15%
Amendment to Application

Dear Dr. Chambers:

Please find enclosed response to the FDA request of January 26, 2005 for an update on the Chemistry, Manufacturing and Controls section concerning the progress of the _____ commitment.

Please find enclosed two review copies and one archive copy of this amendment submission. A field copy has been sent to the Dallas office.

If you have any questions or comments concerning this amendment, please contact me via telephone at 817-551-4877 or via facsimile at 817-551-4630.

Sincerely

Michael E Pfleger

Appears This Way
On Original

Michael Pfleger
Senior Director Regulatory Affairs

Encl.

RECEIVED
FEB 0 8 2005
MEGA / CDER

RECEIVED
FEB 0 2 2005
OGD / CDER

Alcon
RESEARCH, Ltd.

6201 South Freeway
Fort Worth, Texas 76134-2099
(817) 293-0450

January 20, 2005

N-000(BC)

Dr. Wiley Chambers
Division of Analgesic, Anti-Inflammatory
and Ophthalmic Drug Products
CDER, HFD-550
Food and Drug Administration
Document Control Room
9201 Corporate Blvd.
Rockville, Maryland 20850

RE: NDA 21-764 Brimonidine Tartrate Ophthalmic Solution, 0.15%
Amendment to Application

Dear Dr. Chambers:

Please find enclosed response to the request of December 17, 2004 for additional Chemistry, Manufacturing and Controls information.

Please find enclosed two review copies and one archive copy of this amendment submission. A field copy has been sent to the Dallas office.

If you have any questions or comments concerning this amendment, please contact me via telephone at 817-551-4877 or via facsimile at 817-551-4630.

Sincerely

Michael Pfleger
Senior Director Regulatory Affairs

Encl.

Alcon
RESEARCH, Ltd.

6201 South Freeway
Fort Worth, Texas 76134-2099
(817) 293-0450

January 20, 2005

Dr. Wiley Chambers
Division of Analgesic, Anti-Inflammatory
and Ophthalmic Drug Products
CDER, HFD-550
Food and Drug Administration
Document Control Room
9201 Corporate Blvd.
Rockville, Maryland 20850

RE: NDA 21-764 Brimonidine Tartrate Ophthalmic Solution, 0.15%
Amendment to Application

Dear Dr. Chambers:

Please find enclosed response to the FDA request of January 7, 2005 for additional information on the PK data analysis calculation of the 90% confidence intervals.

With regard to the current status of the patent lawsuit between Allergan and Alcon concerning this application, we expect that judgement in this case will be received after the February 28, 2005 PDUFA date.

Please find enclosed two review copies and one archive copy of this amendment submission. A field copy has been sent to the Dallas office.

If you have any questions or comments concerning this amendment, please contact me via telephone at 817-551-4877 or via facsimile at 817-551-4630.

Sincerely

Michael C Pfleger

DUPLICATE

Michael Pfleger
Senior Director Regulatory Affairs

Encl.

DUPLICATE

Alcon
RESEARCH, Ltd.

6201 South Freeway
Fort Worth, Texas 76134-2099
(817) 293-0450

January 3, 2005

Dr. Wiley Chambers
Division of Analgesic, Anti-Inflammatory
and Ophthalmic Drug Products
CDER, HFD-550
Food and Drug Administration
Document Control Room
9201 Corporate Blvd.
Rockville, Maryland 20850

N-000(BC)
ORIG AMENDMENT

RECEIVED
JAN 0 6 2005
MEGA / CDER

RE: NDA 21-764 Brimonidine Tartrate Ophthalmic Solution, 0.15%
Amendment to Application

Dear Dr. Chambers:

Please find enclosed response to the request of November 22, 2005 for additional Chemistry, Manufacturing and Controls information.

Please find enclosed two review copies and one archive copy of this amendment submission. A field copy has been sent to the Dallas office.

If you have any questions or comments concerning this amendment, please contact me via telephone at 817-551-4877 or via facsimile at 817-551-4630.

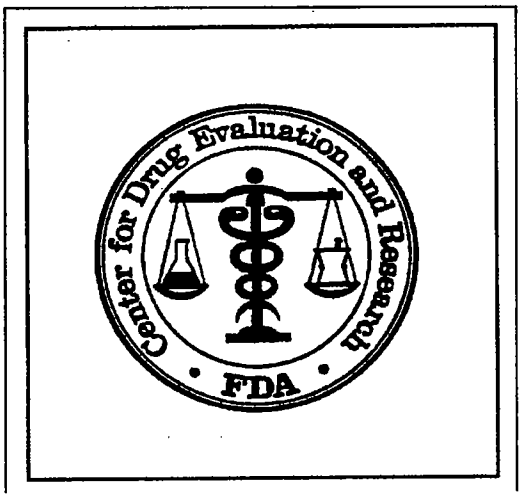
Sincerely

Appears This Way
On Original

Michael Pfleger
Senior Director Regulatory Affairs

Encl.

FACSIMILE TRANSMISSION
RECORD



From: Lin Qi, Ph.D.

Division of Anti-Inflammatory, Analgesic
and Ophthalmic Drug Products, HFD-550

Phone 301-827-2526
Fax 301-827-2531

Date: 12/17/04

To:

Name Mr. Michael Pfleger
Company Alcon, Inc.
City Fort Worth State TX
Phone # 817-551-4877

FAX # 817-551-4630

Number of Pages (INCLUDING COVER PAGE) _2_

Please telephone (301) 827-2040 IMMEDIATELY if re-transmission is necessary.

Appears This Way
On Original

NDA 21-764
Brimonidine Tartrate Ophthalmic Solution, 0.15%

The following 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

1. The "Certificate of Analysis for Brimonidine Tartrate Analytical Reference Standard, [redacted] (Section 3.2.S.5) shows that the "Date of Analysis is 11/17 [redacted] and the "Expiration Date is 11/17/ [redacted] Please clarify if the expiration dating period of [redacted] years is supported by stability data. What is the retest interval for the brimonidine tartrate reference standard? What are the storage conditions of brimonidine tartrate reference standard?

2. The Brimonidine Tartrate Non-aqueous Titration Curves are illegible. Provide the test method and a representative result of the "Assay by Titration".

3. It is stated in Section 3.2.S.5 that [redacted] What other similarly qualified reference standards are used for routine analysis?

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On Original

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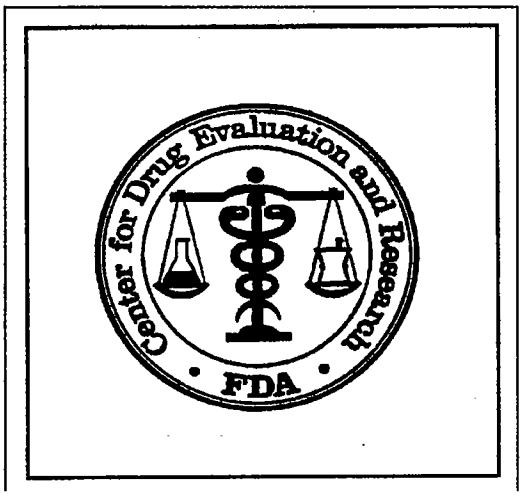
RECORD



From: Lin Qi, Ph.D.

Division of Anti-Inflammatory, Analgesic
and Ophthalmic Drug Products, HFD-550

Phone 301-827-2526
Fax 301-827-2531

Date: 11/22/04

To:

Name Mr. Michael Pfleger
Company Alcon, Inc.
City Fort Worth State TX
Phone # 817-551-4877

FAX # 817-551-4630

Number of Pages (INCLUDING COVER PAGE) _2_

Please telephone (301) 827-2040 IMMEDIATELY if re-transmission is necessary.

Appears This Way
On Original

NDA 21-764
Brimonidine Tartrate Ophthalmic Solution, 0.15%

The following 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

1. Please include acceptance criterion and test for [redacted] in the drug substance specification.

2. Because the 1% solution of the drug substance is "colorless to pale yellow" and "clear to essentially clear", the observations on color and clarity respectively, instead of pass or fail, should be described in the release and stability testing of the drug substance.

3. Please clarify if the color and clarity of the 1% drug substance solution change with time.

4. According to ICH Q6A, the identity test in the drug product solely by the chromatographic retention time is not specific. Please add a second identity test in the drug product specification.

MEMORANDUM

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

CLINICAL INSPECTION SUMMARY

DATE: 11/18/04

TO: Raphael Rodriguez, Project Manager
Rhea Lloyd, M.D., Clinical Reviewer
Division of Anti-inflammatory, Analgesic, and Ophthamological Drug Products
HFD-550

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

FROM: Dianne Tesch, Consumer Safety Officer

SUBJECT: Evaluation of Clinical Inspections

NDA: 21-764

APPLICANT: Alcon

DRUG: Brimonidine tartrate ophthalmic solution, 0.15%

CHEMICAL CLASSIFICATION: 3S

THERAPEUTIC CLASSIFICATION: Standard review

INDICATION: Reduction of intra-ocular hypertension in patients with open-angle glaucoma and/or ocular hypertension for whom single agent therapy provides insufficient intraocular pressure reduction.

CONSULTATION REQUEST DATE: 6/23/04

ACTION GOAL DATE: January 15, 2005

I. BACKGROUND:

The primary objective of this study is to compare the safety and efficacy of Brimonidine

tartrate ophthalmic solution, 0.15%, to that of Alphagan®P, 0.15% in patients with open angle glaucoma or ocular hypertension. Brimonidine tartrate is a selective alpha-2-adrenergic agonist that is effective for the treatment of open angle glaucoma. It reduces aqueous humor and increases uveoscleral outflow. The study compares two formulations of brinonidine tartrate, an already marketed drug. The Alcon study was slightly more complicated than a similar study done at the same time in that the protocol required three measurements of intraocular pressure at each visit. Dr. Wirta's site was one of those chosen by the sponsor to do endothelial photos so the assignment included special instructions to assure that photos were taken, and that copies were available on site.

I. RESULTS (by protocol/site):

NAME	CITY	STATE	ASSIGNED DATE	RECEIVED DATE	CLASSIFICATION
David Wirta	Newport Beach	CA	8/12/04	10/12/04	NAI

A. Protocol #C-02-49 "A Three Month, Randomized, Double-Masked, Parallel Group, Primary Therapy Study, with a Planned Nine Month Extension, of the Safety and IOP Lowering Efficacy of Brimonidine Tartrate Ophthalmic Solutio, 0.15% Compared to Alphagan®P, 0.15% in Patients with Open Angle Glaucoma or Ocular Hypertension".

1. Site #1 David Wirta, M.D., Newport Beach, CA. The data were acceptable.

   a. There were thirty eight subjects enrolled at the site. Thirty three of them experienced various adverse events. Approximately one third of the records were reviewed in depth. There was concurrence between the source documents and the data reported to the sponsor.

   b. There were no limitations to the inspection.

   c. There did not appear to be any under reporting of adverse events. There were no significant protocol violations. Records were available and organized.

II. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

There did not appear to be any deficiencies in the operation overseen by Dr. David Wirta that would affect the integrity or reliability of the data.

Routine surveillance is recommended.

Dianne Tesch, Consumer Safety Officer

CONCURRENCE:

Supervisory comments

Leslie K. Ball, M.D.
Branch Chief
Good Clinical Practice Branch 2
Division of Scientific Investigations

DISTRIBUTION:
NDA 21-764

HFD-45/Division File / Reading File 10571
HFD-550/ Rodriguez Program Management Staff (electronic copy)
HFD-47 Ball
HFD-47/ Tesch
HFD-47/Petague GCPB2 Files # 10571

DUPLICATE

RECEIVED
OCT 18 2004
MEGA / CDER

Alcon RESEARCH, Ltd.
6201 South Freeway
Fort Worth, Texas 76134-2099
(817) 293-0450

October 15, 2004

Michael E. Pfleger
Senior Director, Regulatory Affairs
Telephone: 817/551-4877
Telefax: 817/551-4630

N-000 (b)
NEW CORRESP

Dr. Wiley Chambers
Division of Analgesic, Anti-Inflammatory
and Ophthalmic Drug Products
CDER, HFD-550
Food and Drug Administration
Document Control Room
9201 Corporate Blvd.
Rockville, Maryland 20850

RE: NDA 21-764 Brimonidine Tartrate Ophthalmic Solution, 0.15%
Amendment to Application

Dear Dr. Chambers:

Please find enclosed response to the request of October 7, 2004 for additional information to address administrative comments.

Please find enclosed two review copies and one archive copy of this amendment submission. A field copy has been sent to the Dallas office.

If you have any questions or comments concerning this amendment, please contact me via telephone at 817-551-4877 or via facsimile at 817-551-4630.

Sincerely,

Michael Pfleger
Senior Director Regulatory Affairs

Appears This Way
On Original

Enclosures

Alcon
RESEARCH, Ltd.

6201 South Freeway
Fort Worth, Texas 76134-2099
(817) 293-0450

September 2, 2004

Dr. Wiley Chambers
Division of Analgesic, Anti-Inflammatory
and Ophthalmic Drug Products
CDER, HFD-550
Food and Drug Administration
Document Control Room
9201 Corporate Blvd.
Rockville, Maryland 20850

N 000 (C)
NEW CORRESP

RECEIVED
SEP 0 7 2004
MEGA/CDER

RE: NDA 21-764 Brimonidine Tartrate Ophthalmic Solution, 0.15%
Notification of Court Actions

Dear Dr. Chambers:

Please find enclosed copy of the **COMPLAINT FOR PATENT INFRINGEMENT** filed by Allergan, Inc. and Allergan Sales, LLC against Alcon Laboratories and Alcon Research, Ltd. on August 24, 2004 regarding Patent Nos. 6,641,834 and 6,673,337.

If you have any questions or comments concerning this amendment, please contact me via telephone at 817-551-4877 or via facsimile at 817-551-4630.

Sincerely

Michael E. Pfleger

Michael E. Pfleger
Senior Director Regulatory Affairs

Appears This Way
On Original

Encl.

August 25, 2004

Alcon
RESEARCH, Ltd.

6201 South Freeway
Fort Worth, Texas 76134-2099
(817) 293-0450

Wiley A. Chambers, MD
Deputy Director, DAAODP
FDA / CDER, HFD-550
Document Control Room
9201 Corporate Blvd.
Rockville, Maryland 20850

N.000(SU)

ORIG AMENDMENT

RECEIVED
AUG 2 6 2004
MEGA/CDER

RE: NDA 21-764
Brimonidine Tartrate Ophthalmic Solution, 0.15%
Four – Month Safety Update

RR
9/7/04
NAI

Dear Dr. Chambers

Pursuant to 21 CFR δ 314,50(d)(5)(vi)(b), enclosed please find the four-month safety update for the above referenced NDA. This update includes human safety information on clinical trial C-02-49. Clinical trial C-02-49 is a three-month, randomized, double-masked, parallel group, primary therapy study with a planned nine-month extension. The data included in this submission includes data following the submission of the original NDA to the conclusion of the twelve-month study. This study is now completed.

A revised draft package insert, taking into account the additional safety information on Brimonidine Tartrate Ophthalmic Solution, 0.15% is also enclosed with this update.

If you have any questions or comments concerning this amendment, please contact me via telephone at 817-551-4877 or via facsimile at 817-551-4630.

Sincerely,

ORIGINAL

Michael Pfleger
Senior Director, Regulatory Affairs

Encl.

FISH & RICHARDSON P.C., P.A.

3300 Dain Rauscher Plaza
60 South Sixth Street
Minneapolis, Minnesota
55402

Telephone
612 335-5070

Facsimile
612 288-9696

Web Site
www.fr.com

Frederick P. Fish
1855-1930

W.K. Richardson
1859-1951

FR

BOSTON
DALLAS
DELAWARE
NEW YORK
SAN DIEGO
LICON VALLEY
TWIN CITIES
:HINGTON, DC

August 24, 2004

VIA FACSIMILE AND FEDERAL EXPRESS

N-000(CC)
NEW CORRESP

RECEIVED
AUG 2 5 2004
MEGA/CDER

Brian Harvey, M.D., Ph.D
Acting Director
Food and Drug Administration
Office of Drug Evaluation V
Division of Anti-Inflammatory, Analgesic and
Opthalmologic Drug Products
Room S218A
9201 Corporate Blvd.
Rockville, MD 20850

Re: Abbreviated new drug application No. 21-764

Dear Dr. Harvey:

This letter is to notify the United States Food and Drug Administration of the filing of a legal action for patent infringement as required under 21 C.F.R. § 314.107(f)(2). The information required by this rule is as follows:

(i) NDA No. 21-764

(ii) Name of NDA applicant: Alcon, Inc.

(iii) The established name of the drug product (active ingredient, product strength): ALPHAGAN® P (brimonidine tartrate ophthalmic solution) 0.15%.

A certification that an action for patent infringement has been filed in an appropriate court is attached.

Please feel free to contact my office should you have any questions in regard to this notification.

Very truly yours,

MJK

ORIGINAL

Michael J. Kane

MJK/jel
Enclosure
60240223.doc

DUPLICATE

PATENT AMENDMENT

Alcon RESEARCH, Ltd.
6201 South Freeway
Fort Worth, Texas 76134-2099
(817) 293-0450

July 19, 2004

Dr. Wiley Chambers
Division of Analgesic, Anti-Inflammatory
and Ophthalmic Drug Products
CDER, HFD-550
Food and Drug Administration
Document Control Room
9201 Corporate Blvd.
Rockville, Maryland 20850

N-000 (XP)
ORIG AMENDMENT

RECEIVED
JUL 20 2004
MEGA/CDER

RE: NDA 21-764 Brimonidine Tartrate Ophthalmic Solution, 0.15%
Patent Amendment

Dear Dr. Chambers:

Alcon is amending this application to provide the documentation requested in the filing communication letter for this NDA, dated July 1, 2004.

DOCUMENTATION OF NOTIFICATION / RECEIPT OF NOTICE

- In accordance with 21 CFR 314.95(b), Alcon certifies that the notice has been provided to each person identified under 314.95(a) and that the notice met the content requirements under 314.95(c).
- In accordance with 21 CFR 314.95(e), Alcon is providing documentation of receipt of notice by including a copy of the return Receipt for Merchandise for Certified Mail received by patent holders, Allergan, Inc. and Allergan Sales, Inc. on July 12, 2004.

In addition, as requested, Alcon is providing Form FDA 3542a. No relevant patent has been filed for this product.

Please find enclosed two review copies and one archive copy of this amendment submission.

If you have any questions or comments concerning this amendment, please contact me via telephone at 817-551-4877 or via facsimile at 817-551-4630.

Sincerely

Michael E. Pfleger

Appears This Way
On Original

Michael E. Pfleger
Senior Director Regulatory Affairs

Encl.

Alcon
RESEARCH, Ltd.

6201 South Freeway
Fort Worth, Texas 76134-2099
(817) 293-0450

Michael E. Pfleger
Senior Director
Regulatory Affairs

July 6, 2004

Dr. Wiley Chambers
Division of Analgesic, Anti-Inflammatory
and Ophthalmic Drug Products
Central Document Room
Center for Drug Evaluation and Research
Food and Drug Administration
5901-B Ammendale Rd.
Beltsville, MD 20705

N-000-BM

ORIG AMENDMENT

RE: NDA 21-764
Brimonidine Tartrate Ophthalmic Solution, 0.15%
Telephone Amendment: Request for SAS data sets
Resubmission of Electronic Files

Dear Dr. Chambers:

As requested, please find enclosed CD-ROM containing the SAS data sets, format catalogs, and annotated Case Report Forms for the two clinical studies conducted on Brimonidine Tartrate Ophthalmic Solution, 0.15%. Also included is a certification in the CD in .pdf format that the files are virus free.

If you have any questions or comments concerning this amendment, please contact me via telephone at 817-551-4877 or via facsimile at 817-551-4630.

Sincerely,

Michael E. Pfleger
Senior Director, Regulatory Affairs

Appears This Way
On Original

Enclosures

ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 21-764

Alcon Research, Ltd.
Attention: Michael Pfleger,
Senior Director, Regulatory Affairs
6201 South Freeway
Fort Worth, Texas 76134-2099

Dear Mr. Pfleger:

Please refer to your April 27, 2004, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for brimonidine tartrate ophthalmic solution, 0.15%.

We also refer to your submission dated May 11, 2004.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application was filed under section 505(b) of the Act on June 27, 2004, in accordance with 21 CFR 314.101(a).

In our filing review, we have identified the following potential review issues:

1) Patent Information Form FDA 3542a has not been submitted.

2) Evidence of notification to patent holders of the submission of this application has not been submitted.

3) A waiver of evidence of in vivo bioavailability or bioequivalence could not be granted under 21CFR320.22 (b) (1). Not all conditions cited under 21CFR320.22(b)(1) are met by the new product. Although the new product is an ophthalmic solution containing the same active ingredient at the same concentration as the approved product, Alphagan P, it contains different inactive ingredients.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

We also request that you submit the following information:

1) Provide Patent Information Form FDA 3542a.
2) Provide evidence of notification to patent holders of the submission of this application.

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

If you have any questions, call Nancy Halonen, Regulatory Project Manager, at (301) 827-2199.

Sincerely,

{See appended electronic signature page}

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

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

/s/

Wiley Chambers
7/1/04 05:46:45 PM

Appears This Way
On Original

Alcon
RESEARCH, Ltd.

6201 South Freeway
Fort Worth, Texas 76134-2099
(817) 293-0450

June 28, 2004

Dr. Wiley Chambers
Division of Analgesic, Anti-Inflammatory
and Ophthalmic Drug Products
CDER, HFD-550
Food and Drug Administration
Document Control Room
9201 Corporate Blvd.
Rockville, Maryland 20850

RE: NDA 21-764
Brimonidine Tartrate Ophthalmic Solution, 0.15%
Telephone Amendment: Request for SAS data sets

Dear Dr. Chambers:

As requested, please find enclosed CD-ROM containing the SAS data sets, format catalogs, and annotated Case Report Forms for the two clinical studies conducted on Brimonidine Tartrate Ophthalmic Solution, 0.15%. Also included is a certification that the files are virus free.

If you have any questions or comments concerning this amendment, please contact me via telephone at 817-551-4877 or via facsimile at 817-551-4630.

Sincerely,

Michael E. Pfleger
Senior Director, Regulatory Affairs

Enclosures

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 21-764
Trade Name:
Generic Name: Brimonidine Tartrate Ophthalmic Solution, 0.15%
Applicant: Alcon, Inc.
Alcon Research, Ltd.

Date of Application: **April 27, 2004**
Date of Receipt: **April 28, 2004**
Date clock started after UN: N/A
Date of Filing Meeting: **June 15, 2004**
Filing Date: **Jun 27, 2004**
Action Goal Date (optional): **February 25, 2005** User Fee Goal Date: **February 28, 2005**

Indications requested: The reduction of intraocular pressure in patients with open-angle glaucoma and or ocular hypertension for whom single agent therapy provides insufficient intraocular pressure reduction.

Type of Original NDA: (b)(1) _____ **(b)(2) X**
OR
Type of Supplement: (b)(1) _____ (b)(2) _____
NOTE: 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 is a (b)(2) application, complete the (b)(2) section at the end of this review.

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

Form 3397 (User Fee Cover Sheet) submitted: **YES** NO

User Fee Status: Paid **Yes (Refund 10/27/2004)** 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. 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 use that that has not been approved under section 505(b). Examples of a new indication for 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 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 use, please contact the user fee staff.

Is there any 5-year or 3-year exclusivity on this active moiety in either a (b)(1) or a (b)(2) application?

Yes

If yes, explain:

Pertaining to referenced NDA 21-262:
PED expiration June 20, 2005

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**

Is the application affected by the Application Integrity Policy (AIP)? YES **NO**
If yes, explain.

If yes, has OC/DMPQ been notified of the submission? YES **N/A**

- Does the submission contain an accurate comprehensive index? **YES** NO
- Was form 356h included with an authorized signature? **YES** NO
  If foreign applicant, both the applicant and the U.S. agent must sign.
- Submission complete as required under 21 CFR 314.50? **YES** NO
  If no, explain:
- If an electronic NDA, does it follow the Guidance? **N/A** YES NO
  If an electronic NDA, all certifications must be in paper and require a signature.
  Which parts of the application were submitted in electronic format?

  Additional comments:
- If in Common Technical Document format, does it follow the guidance? **N/A** YES NO
- Is it an electronic CTD? N/A YES **NO**
  If an electronic CTD, all certifications must be in paper and require a signature.
  Which parts of the application were submitted in electronic format?

  Additional comments:
- Patent information submitted on form FDA 3542a? YES **NO**
  The applicant submits no patents for this NDA, but will provide the forms necessary.
- Exclusivity requested? **YES, 3 years**
  Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.
- Correctly worded Debarment Certification included with authorized signature? **YES** 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 . . . ."

- Financial Disclosure forms included with authorized signature? **YES** NO
  (Forms 3454 and 3455 must be used and must be signed by the APPLICANT.)

- Field Copy Certification (that it is a true copy of the CMC technical section)? **YES** NO

Refer to 21 CFR 314.101(d) for Filing Requirements

- PDUFA and Action Goal dates correct in COMIS? **YES** NO
  If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

- Drug name/Applicant name correct in COMIS? If not, have the Document Room make the corrections.
  YES

- List referenced IND numbers: **IND 64,330 and NDA 21-262 are referenced.**

- End-of-Phase 2 Meeting(s)? **Yes** **Date: January 29, 2003**
  If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? **NO**
  If yes, distribute minutes before filing meeting.

Project Management

- All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC?
  YES NO

- Trade name (plus PI and all labels and labeling) consulted to ODS/DMETS? YES **NO**
  There will be no trade name submitted.

- MedGuide and/or PPI (plus PI) consulted to ODS/DSRCS? N/A YES **NO**

- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted?
  N/A YES NO

If Rx-to-OTC Switch application:

- OTC label comprehension studies, all OTC labeling, and current approved PI consulted to ODS/DSRCS?
  N/A YES NO

- Has DOTCDP been notified of the OTC switch application? YES **N/A**

Clinical

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

Chemistry

- Did applicant request categorical exclusion for environmental assessment? **YES** NO
  If no, did applicant submit a complete environmental assessment?
  If EA submitted, consulted to Nancy Sager (HFD-357)?
  Establishment Evaluation Request (EER) submitted to DMPQ? **YES** NO

- If a parenteral product, consulted to Microbiology Team (HFD-805)? **YES** NO

ATTACHMENT

MEMO OF FILING MEETING

DATE: June 15, 2004

BACKGROUND:
NDA 21-764 Brimonidine Tartrate Ophthalmic Solution, 0.15% [formulated with polyquaternium-1 as the preservative] is a sterile ocular product containing brimonidine tartrate. The drug product contains the same active ingredient, brimonidine tartrate, in the same concentration, 0.15%, but with a different known preservative, that is the basis of an approved full NDA 21-262 [Alphagan P (brimonidine tartrate ophthalmic solution, 0.15%).
NDA 21-764 contains two studies:

Study C-02-49 : A Three-Month, Randomized, Double-Masked, Parallel Group, Primary Therapy Study, with a planned Nine Month Extension, of the Safety and IOP-lowering Efficacy of Brimonidine Tartrate Ophthalmic Solution, 0.15% Compared to ALPHAGAN P, 0.15% in Patients with POAG or Ocular Hypertension.

Primary Objective - To compare the safety and efficacy of Brimonidine Tartrate Ophthalmic Solution, 0.15% to that of ALPHAGAN P, 0.15%.

Study C-03-01 : A Randomized, Double-Masked, Single-dose Pharmokinetic Crossover Study of Brimonidine Tartrate Ophthalmic Solution, 0.15% and Alphagan P, 0.15% in healthy subjects.

Primary Objective - To assess the extent of systemic exposure to Brimonidine following a single topical dose of Brimonidine Tartrate Ophthalmic Solution, 0.15% or Alphagan P, 0.15% in healthy subjects.

ATTENDEES:
Wiley Chambers, William Boyd, Jennifer Harris, Lucious Lim, Rhea Lloyd, Martin Nevitt, Asoke Mukherjee, Dennis Bashaw, Lei Zhang, Atiar Rahman, Terri Rumble, Carmen DeBellas, Lori Gorski, Mike Puglisi, Raphael Rodriguez

ASSIGNED REVIEWERS:

Discipline	**Reviewer**
Medical:	Rhea Lloyd
Secondary Medical:	William Boyd
Statistical:	Atiar Rahman
Pharmacology:	Asoke Mukherjee
Statistical Pharmacology:	
Chemistry:	Lin Qi
Biopharmaceutical:	Lei Zhang
Microbiology, sterility:	Bryan Riley
DSI:	Diane Tesch
Regulatory Project Management:	Raphael Rodriguez
Other Consults:	DDMAC-Sonny Saini

Per reviewers, are all parts in English or English translation? **YES** NO
If no, explain:

CLINICAL **FILE __X____** REFUSE TO FILE

_____

- Clinical site inspection needed: **YES** NO
- Advisory Committee Meeting needed? YES, date if known _____ **NO**
- 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 YES NO

CLINICAL MICROBIOLOGY NA _____ **FILE __X____** REFUSE TO FILE

_____

STATISTICS **FILE __X____** REFUSE TO FILE

_____

BIOPHARMACEUTICS **FILE ___X____** REFUSE TO FILE

_____

- Biopharm. inspection needed: YES **NO**

PHARMACOLOGY NA _____ **FILE ___X____** REFUSE TO FILE

_____

- GLP inspection needed: YES NO

CHEMISTRY **FILE ___X____** REFUSE TO FILE

_____

- Establishment(s) ready for inspection? YES NO
- Microbiology YES NO

ELECTRONIC SUBMISSION: **N/A**
Any comments:

REGULATORY CONCLUSIONS/DEFICIENCIES:

_____ The application is unsuitable for filing. Explain why:

__X__ **The application submitted appears to be well organized and indexed. The application appears to be suitable for filing.**

_____ No filing issues have been identified.

__X__ **Filing issues to be communicated by Day 74.**

ACTION ITEMS:

1. If RTF, notify everybody who already received a consult request of the RTF action. Cancel the EER.

2. 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.

3. **Document filing issues conveyed to applicant by Day 74.**

Appendix A to NDA Regulatory Filing Review

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

(1) it relies on literature to meet any of the approval requirements (unless the applicant has a written right of reference to the underlying data)
(2) it relies on the Agency's previous approval, publicly available FDA reviews, or labeling of another drug sponsor's drug product to meet any of the approval requirements (unless application includes written right of reference to data in another sponsor's NDA)
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to supply data that are normally required 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 published general information (e.g., about disease etiology, support for particular endpoints, methods of analysis) or to general knowledge causes the application to be a 505(b)(2) application)
(4) it seeks approval for a change from a product described in an OTC monograph and relies on the monograph to establish the safety or effectiveness of one or more aspects of the drug product for which approval is sought.

Products that may be likely to be described in a 505(b)(2) application include combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations), because a sponsor often owns or has a right of reference for one of the drugs in the combination but not the other.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, please consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

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

1. Does the application reference a listed drug (approved drug)? **YES** NO

   *If "**No**," skip to question 3.*

2. Name of listed drug(s) referenced by the applicant (if any) and NDA/ANDA # :
   Alphagan-P, NDA 21-262

3. (a) Is there a pharmaceutical equivalent(s) already approved? **YES** NO

   (***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**," skip to question 4. Otherwise, answer part (b).*

   (b) Is the approved pharmaceutical equivalent(s) cited as the listed drug(s)? (It or they should be.) **YES** NO

   *If "**Yes**," skip to question 5. Otherwise, answer part (c).*

   (c) Have you conferred with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007)? **YES** NO

   *If "**No**," please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 5.*

4. (a) Is there a pharmaceutical alternative(s) already approved? **YES** NO

   (***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**," skip to question 5. Otherwise, answer part (b).*

   (b) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)? (It or they should be.) **YES** NO

   *If "**Yes**," skip to question 5. Otherwise, answer part (c).*

   (c) Have you conferred with the Director, Division of Regulatory Policy II, YES NO

Office of Regulatory Policy (ORP) (HFD-007)?

If "No," please contact the Director, Division of Regulatory Policy II, ORP.

5. 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"). **New formulation, contains a different known preservative.**

6. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA will refuse-to-file such NDAs (see 21 CFR 314.101(d)(9)). YES **NO**

7. Is 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 should be refused for filing under 21 CFR 314.101(d)(9)). YES **NO**

8. Is the rate at which the product's active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD (see 21 CFR 314.54(b)(2))? If yes, the application should be refused for filing under 21 CFR 314.101(d)(9). YES **NO**

9. Are there certifications for each of the patents listed for the listed drug? **YES** NO

10. Which of the following patent certifications does the application contain? Note that a patent certification must contain an authorized signature. (Check all that apply and identify the patents to which each type of certification was made, as appropriate)

____ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA.

____ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired.

____ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire.

X 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.

The following Patent Data from Orange Book:

Appl No.	Patent No.	Patent Expiration
NDA 21-262	5424078	JUN 13, 2012
NDA 21-262	5424078 PED	DEC 13, 2012
NDA 21-262	6562873	JUL 10, 2021
NDA 21-262	6562873 PED	JAN 10, 2022
NDA 21-262	6627210	JUL 18, 2021
NDA 21-262	6627210 PED	JAN 18, 2022

NDA 21-262	6641834	JUL 28, 2021
NDA 21-262	6641834 PED	JAN 28, 2022
NDA 21-262	6673337	JUL 26, 2021
NDA 21-262	6673337 PED	JAN 26, 2022

*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)].*

____ 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.

____ 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.)

____ Written statement from patent owner that it consents to an immediate effective date upon approval of the application.

11. Did the applicant:

- Identify which parts of the application rely on information (e.g. literature, prior approval of another sponsor's application) that the applicant does not own or to which the applicant does not have a right of reference?

  YES NO

- Submit a statement as to whether the listed drug(s) identified has received a period of marketing exclusivity?

  YES **NO**

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

  N/A **YES** NO

- Certify that it is seeking approval only for a new indication and not for the indications approved for the listed drug if the listed drug has patent protection for the approved indications and the applicant is requesting only the new indication (21 CFR 314.54(a)(1)(iv).?

  N/A YES NO

12. If the (b)(2) applicant is requesting exclusivity, did the applicant submit the following information required by 21 CFR 314.50(j)(4):

- Certification that at least one of the investigations included meets the definition of "new clinical investigation" as set forth at 314.108(a).

YES NO

- A list of all published studies or publicly available reports that are relevant to the conditions for which the applicant is seeking approval.

YES NO

- EITHER

The number of the applicant's IND under which the studies essential to approval were conducted.

IND # 64,330

OR

A certification that it provided substantial support of the clinical investigation(s) essential to approval if it was not the sponsor of the IND under which those clinical studies were conducted?	N/A	YES	NO

13. Has the Associate Director for Regulatory Affairs, OND, been notified of the existence of the (b)(2) application? **YES** NO

Raphael R. Rodriguez
Regulatory Project Manager
DAAODP, HFD-550
(301)827-2090

33 Page(s) Withheld

✓ Trade Secret / Confidential

✓ Draft Labeling

✓ Deliberative Process

Alcon
RESEARCH, Ltd.

6201 South Freeway
Fort Worth, Texas 76134-2099
(817) 293-0450

May 11, 2004

N-000(BC)

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Dr. Wiley Chambers
Division of Analgesic, Anti-Inflammatory
and Ophthalmic Drug Products
CDER, HFD-550
Food and Drug Administration
Document Control Room
9201 Corporate Blvd.
Rockville, Maryland 20850

ORIG AMENDMENT

RE: NDA 21-764 Brimonidine Tartrate Ophthalmic Solution, 0.15%
Amendment to Application

Dear Dr. Chambers:

Please find enclosed response to the request of May 10, 2004 for additional information to address the CMC comments.

Please find enclosed two review copies and one archive copy of this amendment submission. A field copy has been sent to the Dallas office.

If you have any questions or comments concerning this amendment, please contact me via telephone at 817-551-4877 or via facsimile at 817-551-4630.

Sincerely

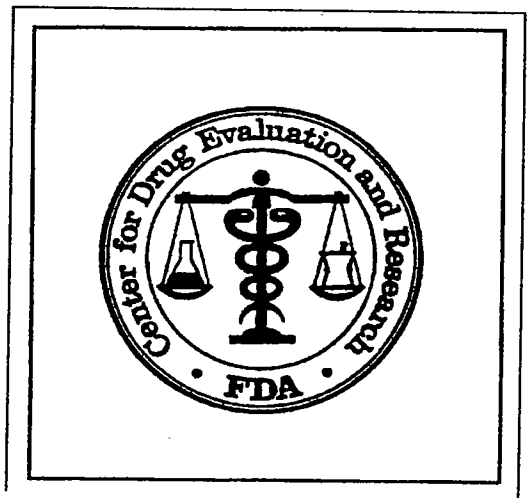
Michael E Pfleger

Michael Pfleger
Senior Director Regulatory Affairs

Encl.

DUPLICATE

FACSIMILE TRANSMISSION RECORD



From: Lin Qi, Ph.D.

Division of Anti-Inflammatory, Analgesic and Ophthalmic Drug Products, HFD-550

Phone 301-827-2526
Fax 301-827-2531

Date: 5/10/04

To:

Name Mr. Michael Pfleger
Company Alcon, Inc.
City Fort Worth State TX
Phone # 817-551-4877

FAX # 817-551-4630

Number of Pages (INCLUDING COVER PAGE) 2

Please telephone (301) 827-2040 IMMEDIATELY if re-transmission is necessary.

Appears This Way
On Original

NDA 21-764
Brimonidine Tartrate Ophthalmic Solution, 0.15%

The following 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

Please provide the contact names, telephone numbers, and fax numbers for the following facilities:

Appears This Way
On Original

6201 South Freeway
Fort Worth, Texas 76134-2099
(817) 293-0450

April 27, 2004

Wiley A. Chambers, MD
Deputy Director Division of Analgesic, Anti-Inflammatory
And Ophthalmic Drug Products, HFD-550
Center for Drug Evaluation and Research
Food and Drug Administration
5901 Unit B Ammendale Road,
Beltsville, MD 20705

RE: NDA 21-764
Brimonidine Tartrate Ophthalmic Solution, 0.15%
NEW DRUG APPLICATION (NDA #21-764; USER FEE ID # 4741)

Dear Dr. Chambers

As an authorized U.S. representative of Alcon, Inc., I hereby submit a New Drug Application (NDA) for Brimonidine Tartrate Ophthalmic Solution, 0.15%. This NDA is being submitted pursuant to 21 CFR§314.54 and Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act. This drug product will be marketed as a prescription product and is indicated for the reduction of intraocular pressure in patient with open-angle glaucoma and or ocular hypertension for whom single agent therapy provides insufficient intraocular pressure reduction. The product will be marked under the established name and a proprietary name is not being submitted.

The user fee (ID # 4741) has been paid for this application. A copy of the user fee cover sheet is provided in Module 1, Section 3.A.5.

Letters of authorization are provided in Module 1, Section 3.A.7. A list of facilities listed in this application is also included as an attachment to the form FDA356h. These facilities listed are ready for inspection.

A true copy of the Chemistry, Manufacturing and Controls information (Quality – Modules 2.3 and 3 has been provided to the Dallas District Office in Dallas, TX.

The application consists of a paper archival copy and the appropriate number of review copies. The submission was prepared in common technical document format in accordance with the following Guidance for Industry:

- M4: Organization of the CTD
- M4Q: The CTD – Quality
- M4S: The CTD – Safety
- M4S: The CTD – Safety Appendices
- M4E: The CTD – Efficacy
- Submitting Marketing Applications According to the ICH-CTD Format – General Considerations

If you have any questions or comments concerning this submission, please contact me by telephone at 817-551-4877 or via facsimile at 817-551-4630.

Sincerely,

Michael E Pfleger

Michael Pfleger
Senior Director, Regulatory Affairs

Cc. Dallas District Office

Appears This Way
On Original

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

PRESCRIPTION DRUG USER FEE COVER SHEET

Form Approved: OMB No. 0910-0297
Expiration Date: December 31, 2006.

See Instructions on Reverse Side Before Completing This Form

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: http://www.fda.gov/cder/pdufa/default.htm

1. APPLICANT'S NAME AND ADDRESS

Alcon, Inc.
P.O. Box 62
Bosch 69
CH-6331, Hunenberg
Switzerland

2. TELEPHONE NUMBER *(Include Area Code)*

(817) 551-4877

3. PRODUCT NAME

Brimonidine Tartrate Ophthalmic Solution, 0.15%

4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER

NDA 21-764

5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?

☑ YES ☐ NO

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

IF RESPONSE IS 'YES', CHECK THE APPROPRIATE RESPONSE BELOW:

☑ THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.

☐ THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:

_____
(APPLICATION NO. CONTAINING THE DATA).

6. USER FEE I.D. NUMBER

4741

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE **EXCLUSIONS**? IF SO, CHECK THE APPLICABLE EXCLUSION.

☐ A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 *(Self Explanatory)*

☐ A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE *(See item 7, reverse side before checking box.)*

☐ THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act *(See item 7, reverse side before checking box.)*

☐ THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY *(Self Explanatory)*

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? ☐ YES ☑ NO

(See Item 8, reverse side if answered YES)

Public reporting burden for this collection of information is estimated to average 30 minutes 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:

Department of Health and Human Services
Food and Drug Administration
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

and

Food and Drug Administration
CDER, HFD-94
12420 Parklawn Drive, Room 3046
Rockville, MD 20852

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.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
[signature]	Senior Director, Regulatory Affairs	03/12/2004

FORM FDA 3397 (12/03)

PSC Media Arts (301) 443-1090 EF

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: August 31, 2005
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Alcon, Inc.	April 27, 2004
TELEPHONE NO. *(Include Area Code)*	**FACSIMILE** *(FAX)* **Number** *(Include Area Code)*
817-551-4877	817-551-4630
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):*	**AUTHORIZED U.S. AGENT NAME & ADDRESS** *(Number, Street, City, State, ZIP Code, telephone & FAX number)* **IF APPLICABLE**
Alcon, Inc. P.O. Box 62 Bosch 69 CH-6331, Hunenberg Switzerland	Alcon Research, Ltd. R7-18 6201 South Freeway Fort Worth, Texas 76134-2099 Phone: 817-551-4877 Fax: 817-551-4630

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* NDA 21-764

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Brimonidine Tartrate Ophthalmic Solution, 0.15%	

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*

CODE NAME *(If any)*

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Solution	0.15%	Ophthalmic

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(PROPOSED) INDICATION(S) FOR USE:

adicated for lowering IOP in patients with OH or OAG

APPLICATION INFORMATION

APPLICATION TYPE *(check one)* ☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94) ☐ BIOLOGICS LICENSE APPLICATION (21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☐ 505 (b)(1) ☒ 505 (b)(2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

Name of Drug _____ Holder of Approved Application _____

TYPE OF SUBMISSION *(check one)* ☒ ORIGINAL APPLICATION ☐ AMENDMENT TO APENDING APPLICATION ☐ RESUBMISSION ☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION
Original submission

PROPOSED MARKETING STATUS *(check one)* ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 55 THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

DUPLICATE

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

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MEGA/CDER

This application contains the following items: *(Check all that apply)*	
☒	1. Index
☒	2. Labeling *(check one)* ☒ Draft Labeling ☐ Final Printed Labeling
☒	3. Summary (21 CFR 314.50 (c))
☒	4. Chemistry section
☒	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
☐	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
☐	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
☒	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
☒	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
☐	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
☒	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
☐	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
☒	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
☒	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
☒	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
☒	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
☒	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
☐	15. Establishment description (21 CFR Part 600, if applicable)
☒	16. Debarment certification (FD&C Act 306 (k)(1))
☒	17. Field copy certification (21 CFR 314.50 (l)(3))
☒	18. User Fee Cover Sheet (Form FDA 3397)
☒	19. Financial Information (21 CFR Part 54)
☐	20. OTHER *(Specify)*

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act Section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE:
Michael E Pfleger	Michael E. Pfleger, Senior Director, Regulatory Affairs	04/27/04

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
6201 South Freeway R7-18 Fort Worth, Texas 76134-2099	(817) 551-4877

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Department of Health and Human Services
Food and Drug Administration
CDER, HFD-99
1401 Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CDER (HFD-94)
12229 Wilkins Avenue
Rockville, MD 20852

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MEETING MINUTES

MEETING DATE: 1/29/03 TIME: 11:30 am LOCATION: CORP. S300

IND # 64,330 Meeting Request Submission Date – 10/10/02
Date Scheduled – 10/16/02
Meeting Packages Submitted – 12/12/02

DRUG: Brimonidine Tartrate Ophthalmic Solution 0.15%
SPONSOR: Alcon, Inc.
TYPE OF MEETING: End of Phase II

FDA PARTICIPANTS:
Wiley Chambers/ Deputy Division Director
Lee Simon/ Division Director
William Boyd/ Clinical Team Leader
Jennifer Harris/ Medical Officer
Matthew Feinsod/ Staff Fellow
Lucious Lim/ Medical Officer
Mike Puglisi/ Project Manager
Lori Gorski/ Project Manager
Raphael Rodriguez/ Project Manager
Shawn Khorshidi/ Chemist
Linda Ng/ Chemistry Team Leader
M. Atiar Rahman/ Biostatistician
Chandra Chaurasia/ PK Reviewer
Dennis Bashaw/ PK Team Leader
Josie Yang/ Pharm/Tox Team Leader
Terri Rumble/ Office ADRA
Jonca Bull/ Office Director

INDUSTRY PARTICIPANTS:
Michael Pfleger/ Senior Director, Regulatory Affairs
Scott Krueger/ Vice President, Regulatory Affairs
Theresa Landry/ Clinical Development
Michael Bergamini/ Vice President, Pharmaceutical Development

MEETING OBJECTIVES:
To discuss the Sponsor's plans to develop a formulation of brimonidine tartrate ophthalmic solution, 0.15% for the indication of reduction of intraocular pressure in patients with open-angle glaucoma or ocular hypertension.

QUESTIONS FOR DISCUSION:

1) As discussed in section 2.1.P.2 Product Development, Alcon's formulation of brimonidine tartrate ophthalmic solution, 0.15% has been designed to pharmaceutically equivalent to ALPHAGAN® P (brimonidine tartrate ophthalmic solution, 0.15%). The proposed drug product contains identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, in identical dosage forms, but not containing the same inactive ingredients, in that the Alcon product employs POLYQUAD®, rather than Purite®, as the preservative. Does the Division agree that the two formulations are pharmaceutically equivalent?

Agency Response: *Yes, per 21 CFR 320.1(C), they are pharmaceutically equivalent.*

2) Alcon is intending to manufacture —, 5 mL, 10 mL and 15 mL presentations of the product. The bottle design and headspace for the 5 mL, 10 mL and 15 mL presentations are sufficiently similar to justify a — protocol. Therefore,

Agency Response:

a.

b. *Determination of the expiration dating period for all proposed presentations will depend upon the quality of the stability data.*

3) As these Primary Stability Lots will be manufactured at commercial scale, Alcon intends to identify these lots in our post-approval stability protocol for purpose of extending the expiry period of the product via the annual report process using real time data from these lots. Does the Division support the use of these lots for this purpose?

Agency Response: *Yes, your proposal is acceptable.*

Additional CMC Comments:

Drug substance

1. *Determination of acceptance criteria should be based upon the actual results of release and stability data.*

Drug Product

2. *For ID testing, please include one specific or two non-specific tests.*

3. *Adequate acceptance criteria should be proposed for the impurities in the drug product specification. The phrase "Report Data" is not acceptable.*

4. *The proposed ——— for the preservative POLYQUAD should be justified by adequate supporting data.*

5. *A quantitative color test with acceptance criterion should be proposed for both the drug substance solution (1%) and the drug product formulation.*

6. *For the ——— matter, in addition to the proposed initial and at end of shelf-life testing, we recommend that another testing time point be included (e.g. at 12 month).*

7. *In the stability program, the testing time intervals for the refrigerated condition ——— should be identical to the long term testing time points, i.e. 12, 26, 39, 52, 78 and 104 weeks.*

4) Alcon believes that the safety of brimonidine is established, and intends to file our NDA as a 505(b)2 application using ALPHAGAN® (NDA 20-613) and/or ALPHAGAN® P (NDA 21-262) as the reference product(s), based on the Agency's previous finding of safety and/or effectiveness for the drug.

The proposed product meets the identical compendial or other applicable standards such as identity, strength, quality, purity, etc.

In order to confirm the safety of our POLYQUAD® preserved formulation, Alcon has conducted a three-month topical ocular study in pigmented rabbits, substantiating the safety of the proposed product relative to the approved products.

The safety of the preservative, POLYQUAD®, has been previously established, as previously submitted in NDA 20-809. Nonclinical safety data supporting POLYQUAD® will be included within our 505(b)2 application.

Alcon considers that the three-month "bridging study" with the proposed product formulation in a pigmented rabbit strain, accompanied by nonclinical safety data supporting the POLYQUAD® preservative, together with the Agency's previous finding of safety and/or effectiveness for ALPHAGAN® and ALPHAGAN® P are sufficient to support the approvability of our formulation. Does the Division concur?

Agency Response: *Yes, the Division concurs.*

5) In addition to summarizing the preclinical pharmacokinetics of brimonidine from the literature, Alcon intends to include the following data in the NDA from our own studies:

   A. An ocular uptake study in pigmented rabbits using the proposed formulation.

   B. Toxicokinetic analyses on plasma samples from the three-month topical ocular toxicology study in rabbits using validated bioanalytical methods.

   Does the Division have any comments concerning the sufficiency of the intended preclinical pharmacokinetic plan for supporting the approvability of our NDA?

   Agency Response: *No, the proposed studies are adequate.*

6) Based upon earlier informal discussions with the Division, Alcon had intended to replicate the clinical plan fo

   herefore, Alcon would like to identify and confirm a clinical plan that would support the approval of our POLYQUAD® - preserved Brimonidine Tartrate Ophthalmic Solution, 0.15% formulation and also provide an AB therapeutic equivalency rating to ALPHAGAN® P.

   a) As reflected in the filing of IND 64,330, Alcon plans to conduct a 3-month efficacy study with a nine-month safety extension versus ALPHAGAN® P (Protocol C-02-49). Both products would be dosed TID. Approximately 200 patients per arm will be enrolled into this study. Would this clinical safety and efficacy study, by itself (excluding any clinical pharmacokinetic requirements), adequately support the clinical requirements for supporting our objective?

   Agency Response: *The design appears appropriate; decisions regarding approval can only be made after review of the NDA.*

b) If the answer to 6.A. is no, in what way is this single long-term study inadequate for supporting a 505(b)(2) approval?

Agency Response: *N/A*

c) If the patient exposure is insufficient, does the Division agree that additional patient exposure could be obtained from either increasing the size of the C-02-49 study or by conducting a second three-month study (C-02-48)?

Agency Response: *Yes.*

7) Protocol C-02-49 is being set up as a 3-month efficacy study with a 9-month safety extension with ALPHAGAN® P as the designated comparator. As both products will be dosed TID, Alcon has elected to measure IOP at 8 am, 10 am, and 5 pm at Week 2, Week 6, and Month 3. Our intention is to file our NDA based upon the three-month efficacy analysis utilizing Mean IOP as the primary efficacy parameter. It is our understanding that the criteria for demonstrating equivalence is the majority of confidence intervals being within 1 mm Hg and all confidence intervals being within 1.5 mm Hg. Would the Division please confirm the appropriateness of the IOP measurement times as well as the criteria for approval?

Agency Response: *IOP measurements as defined are acceptable endpoints. Decisions on approval can only be made after review of the NDA.*

8) The safety parameters to be evaluated in C-02-49 include at baseline: a urine pregnancy test, logMAR visual acuity, slit lamp biomicroscopy, dilated fundus exam, pulse/blood pressure, automated perimetry, endothelial cell density, and pachymetry. All baseline assessments will be repeated at the Month 12/Exit examination. The 3-month analysis will not include treatment data for automated perimetry, endothelial cell density, and pachymetry. The other safety parameters, logMAR visual acuity, slit lamp biomicroscopy, dilated fundus exam and pulse/blood pressure will be assessed during the 3-month treatment interim and their data will be included in the Month 3 report. Does the Division have any comments concerning the sufficiency of the design of C-02-49 for adequately demonstrating the clinical safety or for supporting the objective of our clinical development program?

Agency Response: *See M.O. comments regarding C-02-49 (previously transmitted to Alcon) If submission is to be based on 6 month data, all assessments at 12 months should also be performed at 6 months.*

9) Alcon intends to meet the requirements for demonstrating the bioequivalence of POLYQUAD®-preserved Brimonidine Tartrate Ophthalmic Solution to ALPHAGAN® P via 21 CFR§320.21(e) per 21 CFR§320.24(b)(4) through the conduct of clinical study C-02-49 or a 3-month clinical study of similar design (C-020-48). Does the Division agree that the conduct of clinical study C-02-49 (or C-02-48) would meet the requirements for demonstrating bioequivalence of administered POLYQUAD®-preserved Brimonidine Tartrate Ophthalmic Solution to ALPHAGAN® P?

Agency Response: *The trial design(s) are acceptable (once previously transmitted M.O. comments regarding the protocols are incorporated); the study results will need to be reviewed to make a final determination.*

10) Alcon plans to conduct a clinical pharmacokinetic study in healthy adult males and females administered POLYQUAD®-preserved Brimonidine Tartrate Ophthalmic Solution, 0.15% or ALPHAGAN® P (brimonidine tartrate ophthalmic solution), 0.15% in order to support the inclusion of pharmacokinetic information in our product labeling. This study will have a 2-way crossover design and will characterize the steady-state exposure (plasma concentrations) of brimonidine after multiple three-time daily topical ocular doses.

a) Does the Division agree that this proposed study is sufficient to support the inclusion of pharmacokinetic labeling statements within the product labeling for administered POLYQUAD®-preserved Brimonidine Tartrate Ophthalmic Solution, 0.15%? (Section 2.4.2.3)

Agency Response: *Yes, the proposed study is sufficient. The Day 7 blood collection is not necessary. A blood test is needed only at Day 1, up to 12 hours after dosing.*

b) Does the Division agree that this study is not required to support product approval?

Agency Response: *Per 21 CFR 320.22 (b)(3)(iii), the Sponsor must first submit supporting evidence that a PK study isn't needed.*

11) Based upon the discussion of our clinical plans and the associated purpose of each study, would the Division please confirm for which of the clinical studies financial disclosure information should be obtained?

Agency Response: *Financial disclosure information should be submitted for C-02-49 and C-02-48 and any PK study conducted.*

12) Does the Division agree, assuming clinical study C-02-49 or C-02-48 demonstrates therapeutic equivalence, that the proposed clinical plan would result in the assignment of an AB therapeutic equivalency rating of our administered POLYQUAD®-preserved Brimonidine Tartrate Ophthalmic Solution, 0.15% formulation with ALPHAGAN® P (brimonidine tartrate ophthalmic solution, 0.15%)?

Agency Response: *The determination of AB ratings is made by the Office of Generics.*

13) Is the Division aware of any elements of our development plan that have not been discussed that might affect either the fileability or approvability of our proposed 505(b)(2) NDA?

Agency Response: *Not at this time.*

Prepared by: Michael Puglisi
Project Manager
HFD-550

Concurrence by: Wiley A. Chambers, M.D.
Deputy Division Director
HFD-550

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

/s/

Wiley Chambers
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