

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**204251Orig1s000**

**ADMINISTRATIVE and CORRESPONDENCE**  
**DOCUMENTS**

## EXCLUSIVITY SUMMARY

NDA # 204251

SUPPL #

HFD #

Trade Name SIMBRINZA

Generic Name brinzolamide/brimonidine tartrate ophthalmic suspension 1%/0.2%

Applicant Name: Alcon Research, Ltd.

Approval Date, If Known: April 19, 2013

### PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

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

YES  NO

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

505(b)(2)

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

YES  NO

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

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

d) Did the applicant request exclusivity?

YES  NO

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

3 years

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

YES  NO

*Pediatric exclusivity has been granted for brinzolamide*

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

No

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

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

YES  NO

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

## **PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES**

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

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

YES  NO

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

NDA#

NDA#

NDA#

2. Combination product.

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

YES  NO

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

NDA# 20816 Azopt (brinzolamide)

NDA# 20613 Alphagan (brimonidine tartrate)

NDA#

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

IF "YES," GO TO PART III.

**PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS**

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

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If

the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES  NO

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

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

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

YES  NO

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

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

YES  NO

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

YES  NO

If yes, explain:

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

YES  NO

If yes, explain:

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

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"):

Investigation # 1

Study C-10-033-“Three Month Efficacy and Safety Study of a Fixed Combination of Brinzolamide 1%/ Brimonidine 0.2% compared to Brinzolamide 1% and Brimonidine 0.2% All Dosed Three Times Daily in Patients with Open-Angle Glaucoma and/or Ocular Hypertension”

Investigation # 2

Study C-10-039- A Three-Month, Randomized, Double-Masked, Parallel-Group Study with a Planned Three-Month Safety Extension of the Efficacy and Safety of a Fixed Combination of Brinzolamide 1%/Brimonidine 0.2% Compared to Brinzolamide 1% and Brimonidine 0.2% All Dosed Three Times Daily in Patients with Open-Angle Glaucoma and/or Ocular Hypertension”

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 # 106293

YES

!  
!  
! NO   
! Explain:

Investigation #2

!

IND # 106293      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       ! NO   
Explain:      ! Explain:

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

=====

Name of person completing form: Judit Milstein  
Title: Chief, Project Management Staff

Date: April 18, 2013

Name of Office/Division Director signing form: Renata Albrecht, MD

Title: Director, Division of Transplant and Ophthalmology Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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

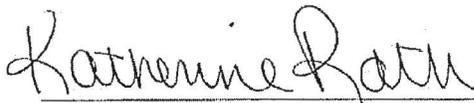
/s/  
-----

JUDIT R MILSTEIN  
04/19/2013

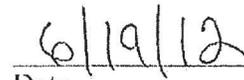
RENATA ALBRECHT  
04/19/2013

**1.3.3. Debarment Certification**

Alcon Research, Ltd. and its affiliated companies (Alcon Pharmaceuticals, Ltd. and Alcon Laboratories, Inc.) hereby certify that it did not and will not use in any capacity the service of any person debarred under section 306 of the Federal Food, Drug and Cosmetic Act in connection with this application.



Katherine Rath  
Assistant Director, Regulatory Affairs  
(817) 302-5912

  
Date

# ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION <sup>1</sup>		
NDA # 204251 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type:
Proprietary Name: SIMBRINZA Established/Proper Name: Brinzolamide/Brimonidine Tartrate 1%/0.2% Dosage Form: Ophthalmic suspension		Applicant: Alcon, Research Agent for Applicant (if applicable):
RPM: Judit Milstein		Division: Transplant and Ophthalmology Products
<p><b><u>NDA and NDA Efficacy Supplements:</u></b></p> <p>NDA Application Type:   <input type="checkbox"/> 505(b)(1)   <input checked="" type="checkbox"/> 505(b)(2)            Efficacy Supplement:   <input type="checkbox"/> 505(b)(1)   <input type="checkbox"/> 505(b)(2)</p> <p>(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). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)</p>		<p><b><u>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</u></b></p> <p>Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s):</p> <p>Alphagan (brimonidine tartrate) 0.2% NDA 21613</p> <p>Provide a brief explanation of how this product is different from the listed drug:</p> <p>This is a combination product of Brinzolamide and brimonidine tartrate.</p> <p>Alcon is both owner of AZOPT (brinzolamide 1%) and the currently approved product.</p> <p><input type="checkbox"/> This application does not reply upon a listed drug.  <input checked="" type="checkbox"/> This application relies on literature.  <input type="checkbox"/> This application relies on a final OTC monograph.  <input checked="" type="checkbox"/> This application relies on findings of safety for the individual component, brimonidine tartrate.</p> <p><b><u>For ALL (b)(2) applications, two months prior to EVERY action, review the information in the 505(b)(2) Assessment and submit the draft<sup>2</sup> to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</u></b></p> <p><b><u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u></b></p> <p><input checked="" type="checkbox"/> No changes   <input type="checkbox"/> Updated   Date of check:</p> <p><b>If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</b></p>
❖ Actions		
<ul style="list-style-type: none"> <li>• Proposed action</li> <li>• User Fee Goal Date is <u>April 19, 2013</u></li> </ul>		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR

<sup>1</sup> The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 5) lists the documents to be included in the Action Package.

<sup>2</sup> For resubmissions, (b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

<ul style="list-style-type: none"> <li>Previous actions (<i>specify type and date for each action taken</i>)</li> </ul>	<input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> <li>If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see <a href="http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf">http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf</a>). If not submitted, explain _____</li> </ul>	<input type="checkbox"/> Received
<ul style="list-style-type: none"> <li>Application Characteristics<sup>3</sup></li> </ul>	
<p>Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority Chemical classification (new NDAs only): 4</p> <p> <input type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch  <input type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch  <input type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC         </p> <p>           NDAs: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510)  <input type="checkbox"/> Restricted distribution (21 CFR 314.520)            Subpart I <input type="checkbox"/> Approval based on animal studies         </p> <p> <input type="checkbox"/> Submitted in response to a PMR  <input type="checkbox"/> Submitted in response to a PMC  <input type="checkbox"/> Submitted in response to a Pediatric Written Request         </p> <p>           BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 601.41)  <input type="checkbox"/> Restricted distribution (21 CFR 601.42)            Subpart H <input type="checkbox"/> Approval based on animal studies         </p> <p>           REMS: <input type="checkbox"/> MedGuide  <input type="checkbox"/> Communication Plan  <input type="checkbox"/> ETASU  <input type="checkbox"/> MedGuide w/o REMS  <input type="checkbox"/> REMS not required         </p> <p>Comments:</p>	
<ul style="list-style-type: none"> <li>BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)</li> </ul>	<input type="checkbox"/> Yes, dates
<ul style="list-style-type: none"> <li>BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)</li> </ul>	<input type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> <li>Public communications (<i>approvals only</i>)</li> </ul>	
<ul style="list-style-type: none"> <li>Office of Executive Programs (OEP) liaison has been notified of action</li> </ul>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> <li>Press Office notified of action (by OEP)</li> </ul>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> <li>Indicate what types (if any) of information dissemination are anticipated</li> </ul>	<input checked="" type="checkbox"/> None <input type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other

<sup>3</sup> Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
<ul style="list-style-type: none"> <li>Is approval of this application blocked by any type of exclusivity?</li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> <li>NDA and BLAs: Is there existing orphan drug exclusivity for the “same” drug or biologic for the proposed indication(s)? <i>Refer to 21 CFR 316.3(b)(13) for the definition of “same drug” for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</i></li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA #                      and date exclusivity expires:
<ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA #                      and date exclusivity expires:
<ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA #                      and date exclusivity expires:
<ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA #                      and date exclusivity expires:
<ul style="list-style-type: none"> <li>NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA #                      and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
<ul style="list-style-type: none"> <li>Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.</li> </ul>	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> <li>Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.</li> </ul>	21 CFR 314.50(i)(1)(i)(A) <input checked="" type="checkbox"/> Verified  21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
<ul style="list-style-type: none"> <li>[505(b)(2) applications] If the application includes a <b>paragraph III</b> certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).</li> </ul>	<input type="checkbox"/> No paragraph III certification Date patent will expire
<ul style="list-style-type: none"> <li>[505(b)(2) applications] For <b>each paragraph IV</b> 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 (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark “N/A” and skip to the next section below (Summary Reviews)).</i></li> </ul>	<input type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month 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?

Yes     No

(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).*

- (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)?

Yes     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 the rest of the patent questions.*

*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?

Yes     No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) 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)).

*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     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 the next section below (Summary Reviews).*

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

<p>(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) 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)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).</p> <p><i>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 the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i></p>	<input type="checkbox"/> Yes <input type="checkbox"/> No
---	--

**CONTENTS OF ACTION PACKAGE**

❖ Copy of this Action Package Checklist <sup>4</sup>	Yes
<b>Officer/Employee List</b>	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list ( <i>approvals only</i> )	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included
<b>Action Letters</b>	
❖ Copies of all action letters ( <i>including approval letter with final labeling</i> )	Approval April 19, 2013
<b>Labeling</b>	
❖ Package Insert ( <i>write submission/communication date at upper right of first page of PI</i> )	
<ul style="list-style-type: none"> <li>• Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.</li> </ul>	April 18, 2013
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	July 3, 2013
<ul style="list-style-type: none"> <li>• Example of class labeling, if applicable</li> </ul>	

<sup>4</sup> Fill in blanks with dates of reviews, letters, etc.

<ul style="list-style-type: none"> <li>❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>)</li> </ul>	<input type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> <li>• Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.</li> </ul>	
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	
<ul style="list-style-type: none"> <li>• Example of class labeling, if applicable</li> </ul>	
<ul style="list-style-type: none"> <li>❖ Labels (<b>full color</b> carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>)</li> </ul>	
<ul style="list-style-type: none"> <li>• Most-recent draft labeling</li> </ul>	April 18, 2013
<ul style="list-style-type: none"> <li>❖ Proprietary Name             <ul style="list-style-type: none"> <li>• Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>)</li> <li>• Review(s) (<i>indicate date(s)</i>)</li> <li>• Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name.</li> </ul> </li> </ul>	August 17, 2012 February 15, 2013 August 9, 2012
<ul style="list-style-type: none"> <li>❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>)</li> </ul>	<input checked="" type="checkbox"/> RPM August 21, 2012 <input checked="" type="checkbox"/> DMEPA Consult to: August 21, 2012 Review: March 14, 2013 <input type="checkbox"/> DMPP/PLT (DRISK) <input checked="" type="checkbox"/> ODPD (DDMAC) Consult to: August 21, 2012 Review: April 9, 2013 <input type="checkbox"/> SEALD <input type="checkbox"/> CSS <input type="checkbox"/> Other reviews
<b>Administrative / Regulatory Documents</b>	
<ul style="list-style-type: none"> <li>❖ Administrative Reviews (<i>e.g., RPM Filing Review<sup>5</sup>/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>)</li> </ul>	Filing Review: August 28, 2012
<ul style="list-style-type: none"> <li>❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte</li> </ul>	April 4, 2013
<ul style="list-style-type: none"> <li>❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment (<i>indicate date</i>)</li> </ul>	April 19, 2013
<ul style="list-style-type: none"> <li>❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>)</li> </ul>	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> <li>❖ Application Integrity Policy (AIP) Status and Related Documents <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a></li> </ul>	
<ul style="list-style-type: none"> <li>• Applicant is on the AIP</li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> <li>• This application is on the AIP             <ul style="list-style-type: none"> <li>○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>)</li> <li>○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>)</li> </ul> </li> </ul>	<input type="checkbox"/> Yes <input type="checkbox"/> No  <input type="checkbox"/> Not an AP action

<sup>5</sup> Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

❖ Pediatrics ( <i>approvals only</i> ) <ul style="list-style-type: none"> <li>• Date reviewed by PeRC <u>March 20, 2013</u> If PeRC review not necessary, explain: _____</li> <li>• Pediatric Page/Record (<i>approvals only, must be reviewed by PERC before finalized</i>)</li> </ul>	<input checked="" type="checkbox"/> Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent ( <i>include certification</i> )	<input checked="" type="checkbox"/> Verified, statement is acceptable
❖ Outgoing communications ( <i>letters, including response to FDRR (do not include previous action letters in this tab), emails, faxes, telecons</i> )	March 18, 2013 January 11, 2013 December 17, 2012 December 14, 2012 December 11, 2012 December 10, 2012 November 19, 2012 August 27, 2012 August 9, 2012 June 29, 2012
❖ Internal memoranda, telecons, etc.	None
❖ Minutes of Meetings	
• Regulatory Briefing ( <i>indicate date of mtg</i> )	<input checked="" type="checkbox"/> No mtg
• If not the first review cycle, any end-of-review meeting ( <i>indicate date of mtg</i> )	<input type="checkbox"/> N/A or no mtg
• Pre-NDA/BLA meeting ( <i>indicate date of mtg</i> )	<input checked="" type="checkbox"/> No mtg
• EOP2 meeting ( <i>indicate date of mtg</i> )	November 15, 2010
• Other milestone meetings (e.g., EOP2a, CMC pilots) ( <i>indicate dates of mtgs</i> )	None
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available ( <i>do not include transcript</i> )	
<b>Decisional and Summary Memos</b>	
❖ Office Director Decisional Memo ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
Division Director Summary Review ( <i>indicate date for each review</i> )	April 19, 2013
Division Deputy Director Summary Review	April 19, 2013
Cross-Discipline Team Leader Review ( <i>indicate date for each review</i> )	April 19, 2013
PMR/PMC Development Templates ( <i>indicate total number</i> )	<input checked="" type="checkbox"/> None
<b>Clinical Information<sup>6</sup></b>	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) ( <i>indicate date for each review</i> )	See CDTL
• Clinical review(s) ( <i>indicate date for each review</i> )	April 9, 2013 August 27, 2012 (Filing Review)
• Social scientist review(s) (if OTC drug) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None

<sup>6</sup> Filing reviews should be filed with the discipline reviews.

❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not ( <i>indicate date of review/memo</i> )	See MO review, Page 8
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers ( <i>indicate date of each review</i> )	<input checked="" type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation ( <i>indicate date of each review</i> )	<input checked="" type="checkbox"/> Not applicable
❖ Risk Management <ul style="list-style-type: none"> <li>REMS Documents and Supporting Statement (<i>indicate date(s) of submission(s)</i>)</li> <li>REMS Memo(s) and letter(s) (<i>indicate date(s)</i>)</li> <li>Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>)</li> </ul>	<input checked="" type="checkbox"/> None
❖ OSI Clinical Inspection Review Summary(ies) ( <i>include copies of OSI letters to investigators</i> )	February 22, 2013 (Review) February 20, 2013-Letter to Investigator February 19, 2013-Letter to Investigator Consult Request: October 16, 2012
<b>Clinical Microbiology</b> <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None
Clinical Microbiology Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None
<b>Biostatistics</b> <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
Statistical Team Leader Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
Statistical Review(s) ( <i>indicate date for each review</i> )	March 15, 2013 August 7, 2012 (Filing Review)
<b>Clinical Pharmacology</b> <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
Clinical Pharmacology Team Leader Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
Clinical Pharmacology review(s) ( <i>indicate date for each review</i> )	March 22, 2013 August 24, 2012 (Filing Review)
❖ DSI Clinical Pharmacology Inspection Review Summary ( <i>include copies of OSI letters</i> )	<input checked="" type="checkbox"/> None

<b>Nonclinical</b> <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
• Supervisory Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
• Pharm/tox review(s), including referenced IND reviews ( <i>indicate date for each review</i> )	April 9, 2013 March 15, 2013 August 17, 2012
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary ( <i>include copies of OSI letters</i> )	<input checked="" type="checkbox"/> None requested
<b>Product Quality</b> <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
• Branch Chief/Team Leader Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
• Product quality review(s) including ONDQA biopharmaceutics reviews ( <i>indicate date for each review</i> )	April 17, 2013 March 13, 2013 October 1, 2012 August 21, 2012
❖ Microbiology Reviews <input type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) ( <i>indicate date of each review</i> ) <input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) ( <i>indicate date of each review</i> )	<input type="checkbox"/> Not needed December 21, 2012 August 9, 2012
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer ( <i>indicate date of each review</i> )	<input checked="" type="checkbox"/> None
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input type="checkbox"/> Categorical Exclusion ( <i>indicate review date</i> )( <i>all original applications and all efficacy supplements that could increase the patient population</i> )	See CMC Review March 13, 2013, Page 107
<input type="checkbox"/> Review & FONSI ( <i>indicate date of review</i> )	
<input type="checkbox"/> Review & Environmental Impact Statement ( <i>indicate date of each review</i> )	

❖ Facilities Review/Inspection	
<input type="checkbox"/> NDAs: Facilities inspections (include EER printout) (date completed must be within <b>2 years</b> of action date) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites <sup>7</sup> )	Date completed: April 17, 2013 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER (date of most recent TB-EER must be within <b>30 days</b> of action date) (original and supplemental BLAs)	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation (check box only, do not include documents)	<input checked="" type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed (per review)

<sup>7</sup> I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

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

/s/  
-----

JUDIT R MILSTEIN  
04/23/2013

From: Milstein, Judit  
To: "[Sharif, Naj](#)"  
Subject: Your NDA 204251-Simbrinza-Information Request  
Date: Monday, March 18, 2013 9:20:00 AM

---

NDA 204251-Simbrinza

Naj,

In order to continue with the timely review of your submission, we request that you provide the following information no later than March 25, 2013.

1. Regarding the two year rat and mouse oral carcinogenicity studies for brinzolamide (summarized in the label drafts and in NDA module 2.6.6), the study reports were not identified either in NDA 204251 or in the NDA for the listed drug. The CDER Carcinogenicity Assessment Committee (CAC)'s review of the study reports was not identified in the NDA or the referenced NDA. Please provide the location of these study reports (e.g. date submitted, file numbers they were submitted to).
2. It is preferable to provide exposure multiples based on systemic AUC data in nonclinical sections 8 and 13. If adequate pharmacokinetic/toxicokinetic data are available, please calculate exposure multiples based on systemic AUC data for label sections 8 and 13, and provide the datasets used to make these calculations.

Please, let me know if you have any question with regard to this request.

Thank you  
Judit Milstein  
Chief, Project Management Staff  
DTOP/OAP/CDER  
Food and Drug Administration  
10903 New Hampshire Avenue  
Building 22, Room 6170  
Silver Spring, MD 20993  
Phone: 301-796-0763  
Fax: 301-796-9881

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

/s/  
-----

JUDIT R MILSTEIN  
03/18/2013  
NDA 204251-Pharm/Tox Information Request



NDA 204251

**INFORMATION REQUEST**

Alcon Research, Ltd.  
Attention: Katherine Rath  
Assistant Director, Regulatory Affairs  
6201 South Freeway (R3-52)  
Fort Worth, TX 76134-2099

Dear Ms. Rath:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Brinzolamide 1%/Brimonidine tartrate 0.2%, suspension.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. Please provide a prompt written response by January 17, 2013, in order to continue our evaluation of your NDA.

We have reviewed your Response to Information Request dated December 14, 2014. Your proposed acceptance criterion of NMT (b) (4) for any unspecified impurity is not justified even though it is based on the minor component brimonidine. Unspecified impurities are intended to include any unknown impurities including leachables and degradation products. As the eye is a sensitive organ, for ophthalmic products intended for delivery to the eye, the Division has consistently recommended the thresholds for any single unspecified impurity be set lower than those in Q3B (R2) for the same dose range. We continue to recommend tightening the proposed acceptance criterion of NMT (b) (4) for any single unspecified impurity. In alignment with your Brimonidine Tartrate Ophthalmic Solution, 0.2% (ANDA # 76-254), **we recommend that the acceptance criterion of this NDA be also set at NMT (b) (4) of brimonidine for any single unspecified impurity.**

If you have any questions, call Althea Cuff, Regulatory Health Project Manager, at (301) 796-4061.

Sincerely,

*{See appended electronic signature page}*

Rapti D. Madurawe, Ph.D.  
Branch Chief, Branch V  
Division of New Drug Quality Assessment II  
Office of New Drug Quality Assessment  
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/  
-----

RAPTI D MADURawe  
01/11/2013

**Date:** December 14, 2012  
**To:** Alcon Research, Ltd.  
**From:** Clinical Reviewer  
**Re:** NDA 204251 (brinzolamide 1%/brimonidine 0.2% ophthalmic suspension)

**Request for Information**

Please, see information request in addition to the ones dated December 10 and 11, 2012.

Please provide the location of the following analyses for the Intent-to-Treat population with LOCF and Per Protocol population observed cases in Studies C-10-033 and C-10-039:

Upper and lower 95% CI for the mean difference in IOP at each time point at the Eligibility Study Visit (i.e. mean IOP of the combination minus brinzolamide and mean IOP of the combination minus brimonidine at 8AM, +2 hrs, + 7 hrs, and +9 hrs at Eligibility 1 Visit [E1] and Eligibility 2 Visit [E2]).

Please provide the location of the following analyses for the Intent-to-Treat population with LOCF and Per Protocol population observed cases in Study C-09-038:

Upper and lower 95% CI for the mean difference in IOP at each time point at the Eligibility Study Visit (i.e. mean IOP of the combination minus brinzolamide, mean IOP of the combination minus brimonidine, and combination minus brinzolamide + brimonidine given concomitantly at 8AM, +2 hrs, +7 hrs, and +9 hrs at Eligibility 1 Visit [E1] and Eligibility 2 Visit [E2]).

If these analyses have not been performed, please submit.

If you have any questions with regards to this information request, please contact me at 301-796-0763.

Thank you  
Judit Milstein  
Chief, Project Management Staff  
Division of Transplant and Ophthalmology Products

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

/s/  
-----

JUDIT R MILSTEIN

12/17/2012

NDA 204251-Clinical Information Request



NDA 204251

**INFORMATION REQUEST**

Alcon Research, Ltd.  
Attention: Katherine Rath  
Assistant Director, Regulatory Affairs  
6201 South Freeway (R3-52)  
Fort Worth, TX 76134-2099

Dear Ms. Rath:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Brinzolamide 1%/Brimonidine tartrate 0.2%, suspension.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. Please provide a prompt written response by January 4, 2013, in order to continue our evaluation of your NDA.

1. In reference to Table 2 in Alcon Technical Procedure PROC-0004824 concerning the HPLC method for assay and related substance analysis:
  - a) Explain how Sensitivity Standard is used as part of the system suitability test;
  - b) Justify why the resolution between the brinzolamide peak and that of the des-ethyl brinzolamide was selected for system suitability despite the fact Impurity <sup>(b) (4)</sup> peak and the <sup>(b) (4)</sup> peak (as shown in Figure 6) seem to be closer to the peak of interest. Furthermore, according to the method robustness studies presented in TDOC-0010126, the resolution between the peaks of brinzolamide and <sup>(b) (4)</sup> is much more susceptible to small variations (they even co-elute under certain conditions) and hence better suited for system suitability tests. We recommend that the resolution requirement be derived from the resolution between the peak of interest and the closest potential interfering peak.
2. In reference of TDOC-0010126 concerning the validation of the HPLC method PROC-0004824:
  - a) Provide acceptance criteria for the parameters in Tables 3 through 7 (such as specificity, linearity, range, and so on);
  - b) Justify the acceptability of the Precision-Repeatability results for brimonidine tartrate and brinzolamide assays. Both <sup>(b) (4)</sup> RSD and <sup>(b) (4)</sup> RSD seem to be high. We recommend the RSD for the assay method to be <sup>(b) (4)</sup>
  - c) According to ICH Q2 (R1), Intermediate Precision is defined as the variation within the same laboratory including day-to-day variation, analyst variation, and

equipment variation. The studies outlined in your report do not meet this requirement as you have provided only the Standard Deviation from either one-level or two-level replicates, which are considered precision-repeatability studies.

- d) Please explain how Sensitivity (LOQ) is calculated. No LOQ data is provided in TDOC-0010126. In addition, we recommend that limit of detection (LOD) be included in the validation protocol when the method is used for impurity limit test.
  - e) We note that a multivariate design of experiments (DOE) study was used in determining the robustness of the HPLC method. In the report, you state that “The results of the DOE establish a design space for the method.” However, it is not clear to us what the design space is on the basis of the results presented in the report. Please confirm: (1) the purpose of the DOE studies was only to evaluate the robustness of the HPLC method, PROC-0004824; (2) the method will be operated under the standard (center point) conditions; and (3) any future changes to the method parameters beyond the target conditions will be subject to standard regulatory post approval procedures.
3. In reference to TDOC-0009927 concerning the validation of PROC-0000689 for the assay of boric acid, please provide acceptance criteria for the parameters to be validated and justify the acceptability of the high y-intercept value (b) (4)

If you have any questions, call Althea Cuff, Regulatory Health Project Manager, at (301) 796-4061.

Sincerely,

*{See appended electronic signature page}*

Rapti D. Madurawe, Ph.D.  
Branch Chief, Branch V  
Division of New Drug Quality Assessment II  
Office of New Drug Quality Assessment  
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/  
-----

RAPTI D MADURAWA  
12/14/2012

**Date:** December 11, 2012  
**To:** Alcon Research, Ltd.  
**From:** Clinical Reviewer  
**Re:** NDA 204251 (brinzolamide 1%/brimonidine 0.2% ophthalmic suspension)

**Request for Information**

Please provide the location of the following analyses for the Intent-to-Treat population with LOCF and Per Protocol population observed cases in Study C-09-038:

Upper and lower 95% CI for the mean difference in IOP at each time point and study visit (i.e. mean IOP of the combination minus brinzolamide, mean IOP of the combination minus brimonidine, and combination minus brinzolamide + brimonidine given concomitantly at 8AM, +2 hrs, + 7 hrs, and +9 hrs at Study Visits Week 2 and Week 6).

If they have not been performed, please submit.

If you have any questions with regards to this information request, please contact me at 301-796-0763.

Thanks  
Judit Milstein  
Chief, Project Management Staff  
Division of Transplant and Ophthalmology Products

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

/s/  
-----

JUDIT R MILSTEIN

12/11/2012

NDA 204251-Clinical request for information

**Date:** December 10, 2012  
**To:** Alcon Research, Ltd.  
**From:** Clinical Reviewer  
**Re:** NDA 204251 (brinzolamide 1%/brimonidine 0.2% ophthalmic suspension)

**Request for Information**

Please provide the location of the following analyses for the Intent-to-Treat population with LOCF and Per Protocol population observed cases in Studies C-10-033 and C-10-039:

Upper and lower 95% CI for the mean difference in IOP at each time point and study visit (i.e. mean IOP of the combination minus brinzolamide and mean IOP of the combination minus brimonidine at 8AM, +2 hrs, + hrs, and +9 hrs at Study Visits Week 2, Week 6, and Month 3).

If they have not been performed, please submit.

If you have any questions with regards to this information request, please contact me at 301-796-0763.

Thanks  
Judit Milstein  
Chief, Project Management Staff  
Division of Transplant and Ophthalmology Products

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

/s/  
-----

JUDIT R MILSTEIN

12/10/2012

NDA 204251-Clinical Information Request



NDA 204251

## INFORMATION REQUEST

Alcon Research, Ltd.  
Attention: Katherine Rath  
Assistant Director, Regulatory Affairs  
6201 South Freeway (R3-52)  
Fort Worth, TX 76134-2099

Dear Ms. Rath:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Brinzolamide 1%/Brimonidine tartrate 0.2%, suspension.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. Please provide a prompt written response by December 14, 2012, in order to continue our evaluation of your NDA.

### Drug Substance

1. The stability tables for brinzolamide batches from (b) (4) are not in English. Provide an English translation of these tables.

### Drug Product

2. In accordance with CFR 314.50 complete description of the commercial scale drug product manufacturing processes should be provided and should include all process parameters. Additionally, notification of all changes including changes to process parameters beyond the ranges/variations provided for in the application should be provided in accordance with 21CFR 314.70. Taking the above into consideration,
  - a) Confirm that the process parameter ranges as provided in the MBR (Master Batch Record) in section 3.2.R supplements the drug product manufacturing process description provided in section 3.2.P.3.3, and that the MBR provides operating ranges/set points for the process parameters not included in section 3.2.P.3.3. The Agency recognizes that changes to non-critical process parameters can usually be managed under the firm's quality system without the need for regulatory review and approval prior to implementation.
  - b) Provide appropriate operating ranges for all the process parameters (e.g. pH, temperature, processing time), instead of open ended settings or justification for the open ended ranges.

c) [Redacted] (b) (4)

3. In reference to Table 3.2.P.3.3-1 where [Redacted] (b) (4)  
is listed as the sole critical process parameter (CPP),

[Redacted] (b) (4)

4. In reference to Tables 3-1, 3-2, and 3-3 in TDOC-0015342 concerning the design space,  
a) Provide appropriate ranges for process parameters listed in 1.4.3, 1.5.2, 1.6.4,  
2.6.8, and 4.3.9.

[Redacted] (b) (4)

5. We recommend the following revisions to the drug product specification in section 3.2.P.5.1.

Tests	Acceptance Criteria Proposed in NDA	Acceptance Criteria FDA Recommendation
Brinzolamide Impurities [Redacted] (b) (4)	[Redacted]	[Redacted] (b) (4)
Brimonidine Impurities [Redacted] (b) (4)		
Any Single Unspecified Impurity Total Impurities		
Particle Size		

6. Submit available stability data for the drug product, including the 12 months data for Stability Lot Nos. 18601-04 and 18600-05 manufactured at the ASPEX facility.

7. The drug product is packaged in (b) (4) containers. The refrigerated (long-term) stability condition you have used is 5°C/35%RH. The ICH Q1A(R2) recommended refrigerated condition is 5°C ± 3 °C. Discuss the reason for instituting a 35% RH control for the refrigerated condition and its potential impact on the stability data.
8. The proposed shelf-life for the drug product is listed as 78 weeks (or 18 months) in Section 3.2.P.8.1 and as (b) (4) Please reconcile.
9. Include a metals test either in the final drug product specification or as an in-process control test in order to avoid the possible contamination of metal particles including (b) (4) through product life-cycle.

If you have any questions, call Althea Cuff, Regulatory Health Project Manager, at (301) 796-4061.

Sincerely,

*{See appended electronic signature page}*

Rapti D. Madurawe, Ph.D.  
Branch Chief, Branch V  
Division of New Drug Quality Assessment II  
Office of New Drug Quality Assessment  
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/  
-----

BALAJEE SHANMUGAM  
11/19/2012



NDA 204251

**FILING COMMUNICATION**

Alcon Research, Ltd.  
Attention: Norma Schafer  
Senior Manager, Regulatory Affairs  
6201 South Freeway (R3-52)  
Fort Worth, TX 76134-2099

Dear Ms. Schafer:

Please refer to your New Drug Application (NDA) dated and received June 19, 2012, received, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for brinzolamide 1%/brimonidine tartrate 0.2% suspension).

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is April 19, 2013.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, midcycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by March 29, 2013.

**PROMOTIONAL MATERIAL**

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI). Submit consumer-directed,

professional-directed, and television advertisement materials separately and send each submission to:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Prescription Drug Promotion (OPDP)  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>. If you have any questions, call OPDP at 301-796-1200.

### **REQUIRED PEDIATRIC ASSESSMENTS**

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We acknowledge receipt of your request for a full waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you of our decision.

If you have any questions, call Judit Milstein, Chief, Project Management Staff at 301-796-0763.

Sincerely,

*{See appended electronic signature page}*

Renata Albrecht, MD  
Director  
Division of Transplant and Ophthalmology Products  
Office of Antimicrobial Products  
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/  
-----

RENATA ALBRECHT  
08/27/2012

**REQUEST FOR OPDP (previously DDMAC) LABELING REVIEW  
CONSULTATION**

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION

**\*\*Please send immediately following the Filing/Planning meeting\*\***

TO: <b>CDER-DDMAC-RPM</b>	FROM: (Name/Title, Office/Division/Phone number of requestor) Judit Milstein (6-0763) Chief, Project Management Staff Division of Transplant and Ophthalmology Products
------------------------------	--

REQUEST DATE August 20, 2012	IND NO.	NDA/BLA NO. N 204251	TYPE OF DOCUMENTS: NDA submission (PLEASE CHECK OFF BELOW)
---------------------------------	---------	-------------------------	---

NAME OF DRUG Simbrinza (brinzolamide/brimonidine tartrate)	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG ophthalmic	DESIRED COMPLETION DATE March 19, 2013
--	------------------------	--------------------------------------	---

NAME OF FIRM: Alcon Research	PDUFA Date: April 19, 2013
---------------------------------	----------------------------

**TYPE OF LABEL TO REVIEW**

<b>TYPE OF LABELING:</b> (Check all that apply) <input checked="" type="checkbox"/> PACKAGE INSERT (PI) <input type="checkbox"/> PATIENT PACKAGE INSERT (PPI) <input checked="" type="checkbox"/> CARTON/CONTAINER LABELING <input type="checkbox"/> MEDICATION GUIDE <input type="checkbox"/> INSTRUCTIONS FOR USE(IFU)	<b>TYPE OF APPLICATION/SUBMISSION</b> <input checked="" type="checkbox"/> ORIGINAL NDA/BLA <input type="checkbox"/> IND <input type="checkbox"/> EFFICACY SUPPLEMENT <input type="checkbox"/> SAFETY SUPPLEMENT <input type="checkbox"/> LABELING SUPPLEMENT <input type="checkbox"/> PLR CONVERSION	<b>REASON FOR LABELING CONSULT</b> <input type="checkbox"/> INITIAL PROPOSED LABELING <input type="checkbox"/> LABELING REVISION
--	--	--

**EDR link to submission:** <\\CDSESUB1\EVSPROD\NDA204251\204251.enx>

**Please Note:** There is no need to send labeling at this time. OPDP reviews substantially complete labeling, which has already been marked up by the CDER Review Team. After the disciplines have completed their sections of the labeling, a full review team labeling meeting can be held to go over all of the revisions. Within a week after this meeting, "substantially complete" labeling should be sent to OPDP. Once the substantially complete labeling is received, OPDP will complete its review within 14 calendar days.

**COMMENTS/SPECIAL INSTRUCTIONS:**

Mid-Cycle Meeting: TBD  
Labeling Meetings: TBD  
Wrap-Up Meeting: TBD

SIGNATURE OF REQUESTER:: Judit Milstein, CPMS

SIGNATURE OF RECEIVER	METHOD OF DELIVERY (Check one) <input type="checkbox"/> eMAIL <input checked="" type="checkbox"/> DARRTS <input type="checkbox"/> HAND
-----------------------	---

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

/s/  
-----

JUDIT R MILSTEIN  
08/21/2012  
NDA 204251-OPDP Consult



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

/s/  
-----

JUDIT R MILSTEIN

08/21/2012

NDA 204251-OSE Consult labels and labeling



IND 106293  
NDA 204251

**PROPRIETARY NAME REQUEST  
CONDITIONALLY ACCEPTABLE**

Alcon Research, Ltd.  
6201 South Freeway (R3-52)  
Fort Worth, TX 76134-2099

ATTENTION: Katherine Rath  
Assistant Director, Regulatory Affairs

Dear Ms. Rath:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act and your New Drug Application (NDA) Application, dated and received, June 19, 2012, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Brinzolamide and Brimonidine Tartrate Ophthalmic Suspension 1%/0.2%.

We also refer to:

- your February 27, 2012, correspondence, received February 28, 2012, requesting review of your proposed proprietary name, Simbrinza, under the IND; and
- your correspondence, dated and received July 3, 2012, requesting review of your proposed proprietary name, Simbrinza, under the NDA.

We have completed our review of the proposed proprietary name, Simbrinza and have concluded that it is acceptable. The proposed proprietary name, Simbrinza, will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you. Additionally, if **any** of the proposed product characteristics as stated in your July 3, 2012, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Karen Townsend, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-5413. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Diana Willard at (301) 796-0833.

Sincerely,

*{See appended electronic signature page}*

Carol Holquist, RPh

Director

Division of Medication Error Prevention and Analysis

Office of Medication Error Prevention and Risk Management

Office of Surveillance and Epidemiology

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/  
-----

CAROL A HOLQUIST  
08/17/2012

**Milstein, Judit**

**From:** Milstein, Judit  
**Sent:** Thursday, August 09, 2012 4:24 PM  
**To:** 'Schafer, Norma, FORT WORTH, Regulatory Affairs'  
**Subject:** NDA 204251-Simbrinza-Request for additional information

NDA 204251  
Simbrinza (brinzolamide 1%/brimonidine tartrate 0.2%)

Norma,

We conducted a preliminary review of the labeling you submitted with your NDA and we are requesting that you provide revised labeling as follows:

1. In the Adverse Reactions section of the Full Prescribing Information (FPI), the terms "adverse events" and "adverse experiences" should be avoided. The term "adverse reactions" should be utilized.
2. As current requirements do not support a pediatric indication, we recommend you replace the text in Section 8.4 Pediatric Use with the following standard language for the Pediatric Use section:

"Safety and effectiveness in pediatric patients below the age of 18 have not been established."

3. Delete the (b) (4) statement that appears at the end of the package insert. This statement is only required for container and carton labels.
4. (b) (4)
5. Please submit draft carton and container mock-ups for (b) (4) the trade 8 mL configurations. Please submit these mock-ups to Module 1.14 of the NDA. We note the images for the SPL state (b) (4) (b) (4). This statement should be removed.
6. White space must be present before each major heading in the Highlights (HL).
7. Patient labeling was not submitted in the application. Therefore, the phrase (b) (4) should be deleted from the Patient Counseling Information Statement at the end of the HL.
8. A horizontal line must separate the Table of Contents (TOC) from the Full Prescribing Information (FPI).
9. The section headings and subheadings in the TOC must match the headings and subheadings in the FPI.

In addition, our statistician is requesting that you address the following comments:

There are issues with converting XPT files with file names that include hyphens i.e. -iop-01.xpt to SAS datasets. The hyphens are not recognized in a manually programmed Proc Copy statement. Please provide the code necessary to convert XPT files with file names that include hyphens to SAS datasets or any appropriate alternative that will address this issue.

As we are just starting the review of this application, there is no urgency on the labeling revisions; However, we would like an expedited response to the statisticians query.

I would appreciate if you could let me know a timeline for the submission of both requests.

Thank you  
Judit Milstein  
Chief, Project Management Staff  
DTOP/OAP/CDER

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

/s/  
-----

JUDIT R MILSTEIN

08/09/2012

NDA 204251-Information Request



NDA 204251

**NDA ACKNOWLEDGMENT**

Alcon Research, Ltd.  
Attention: Katherine Rath  
Assistant Director, Regulatory Affairs  
6201 South Freeway (R3-52)  
Fort Worth, TX 76134-2099

Dear Ms. Rath:

We have received your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: Brinzolamide 1%/Brimonidine tartrate 0.2%, suspension

Date of Application: June 19, 2012

Date of Receipt: June 19, 2012

Our Reference Number: NDA 204251

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on August 18, 2012, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No. 110-85, 121 Stat. 904).

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Transplant and Ophthalmology Products  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to [SecureEmail@fda.hhs.gov](mailto:SecureEmail@fda.hhs.gov). Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, call me at 301-796-0763.

Sincerely,

*{See appended electronic signature page}*

Judit Milstein  
Chief, Project Management Staff  
Division of Transplant and Ophthalmology  
Products  
Office of Antimicrobial Products  
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/  
-----

JUDIT R MILSTEIN

06/29/2012

NDA 204251-Acknowledgment Letter



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration  
Silver Spring MD 20993

IND 106,293

**MEETING MINUTES**

Alcon Research Ltd.  
Attention: Michael C. Son, Ph.D, RAC  
Senior Manager, Regulatory Affairs  
6201 South Freeway, R3-52  
Fort Worth, TX 76134-2099

Dear Dr. Son:

Please refer to your Investigational New Drug Application (IND) file for brinzolamide/brimonidine tartrate ophthalmic suspension.

We also refer to the meeting between representatives of your firm and the FDA on November 15, 2010. The purpose of the meeting was to obtain guidance from all disciplines on the development plan for brinzolamide/brimonidine tartrate ophthalmic suspension.

A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Lori Marie Gorski, Regulatory Health Project Manager, at (301) 796-0722.

Sincerely,

*{See appended electronic signature page}*

Wiley A. Chambers, M.D.  
Acting Director  
Division of Anti-Infective and Ophthalmology Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research

Enclosure: Meeting Minutes

Reference ID: 2879044

Reference ID: 3301238

**MEMORANDUM OF MEETING MINUTES**  
Division of Anti-Infective and Ophthalmology Products

**APPLICATION:** IND 106,293  
**SPONSOR:** Alcon Research, Ltd  
**TYPE OF MEETING:** End of Phase 2

**DRUG:** brinzolamide/brimonidine tartrate ophthalmic suspension  
**INDICATION:** Treatment of inter-ocular pressure (IOP) in patients with open angle glaucoma or ocular hypertension who require adjunctive or replacement therapy due to inadequately controlled IOP

**MEETING DATE:** November 15, 2010  
**TIME:** 9:00 AM  
**LOCATION:** 10903 New Hampshire Ave  
Silver Spring, MD 20993

**FDA PARTICIPANTS**

**Division of Anti-Infective and Ophthalmology Products**

Chuck Bonapace	Clinical Pharmacology Team Leader
William Boyd	Clinical Team Leader
Wiley A. Chambers	Acting Director
Lori Gorski	Project Manager
Jennifer Harris	Clinical Reviewer
Aryun Kim	Clinical Pharmacology Reviewer
Lucious Lim	Clinical Reviewer
Rhea Lloyd	Clinical Reviewer
Martin Nevitt	Clinical Reviewer
Mushifiquir Rashid	Statistical Reviewer
Wendy Schmidt	Pharmacology Toxicology Team Leader
Sonal Wadhwa	Clinical Reviewer
Yan Wang	Statistical Team Leader
Jim Wild	Pharmacology Toxicology Reviewers
Andrew Yu	Chemistry Reviewer

**SPONSOR PARTICIPANTS**

**Alcon Research, Ltd.**

Angela C. Kothe, O.D., Ph.D.	Senior Director, Regulatory Affairs
Paul Nitschmann, M.D.	Vice President, Regulatory Affairs, Pharmaceutical Products
Michael C. Son, Ph.D.	Senior Manager, Regulatory Affairs

Quintus Ngumah, O.D.	Project Head, Glaucoma Development
Richard L. Beckman, M.D.	Vice President, Therapeutic Unit Head, Glaucoma Development
Bhagwati Kabra, Ph.D.	Associate Director, Formulations
Kevin Nugent, B.S.	Associate Director, Regulatory CMC
Nathan S. Teuscher, Ph.D.	Associate Director, Clinical Pharmacology
Brian L. Wiens, Ph.D.	Director, Biostatistics
Tonya Smoot, Ph.D.	Assistant Director, Biostatistics
Theresa A. Landry, Ph.D.	Senior Director, Clinical Trial Management, Pharmaceutical Products
Eric Nimz, Ph.D.	Assistant Director, Biodisposition
Heather S. Floyd, Ph.D.	Pharmaceutical Toxicologist, Preclinical Safety

### **PURPOSE OF THE MEETING**

To obtain guidance from all disciplines on the development plan for brinzolamide/brimonidine tartrate ophthalmic suspension.

### **QUESTIONS**

#### **QUALITY QUESTIONS**

##### ***Quality Question 1***

Alcon intends to use a global qualification strategy for the Brinzolamide/Brimonidine Suspension. With this strategy, Alcon intends to:

- qualify both the Alcon Fort Worth and the Alcon Belgium sites as manufacturing sites to provide global distribution of the product;
- qualify two brinzolamide drug substance manufacturing sources ( (b) (4) and (b) (4) ) and two brimonidine tartrate manufacturing sources ( (b) (4) and (b) (4) ) for Brinzolamide/Brimonidine Suspension;
- qualify LDPE containers with a fill range (b) (4) 10mL for global launch of this product.

A bracketed approach for the manufacturing sites, drug substance sources and container/fill sizes will be used with the primary stability studies as previously presented in Table 5. Does the Agency agree with this approach?

***FDA Response:*** Yes.

***Quality Question 2***

Alcon proposes to perform stability studies in the horizontal orientation alone. Does the Agency agree with this approach?

***FDA Response:*** *Yes, assuming that this is the worst orientation for stability.*

***Quality Question 3***

Alcon proposes to submit the NDA with a minimum of three months accelerated and three months long-term storage stability data. Consistent with ICH Q1E, the proposed shelf life will be no more than twice the available long-term data (i.e., 6 months shelf life for 3 months available data). The application will be amended with additional stability data during the NDA review cycle to support shelf life extension, as appropriate. In addition, comparative stability data for the single entity products (AZOPT and Brimonidine Tartrate Ophthalmic Solution, 0.2%) will also be included as supportive stability data. Does the Agency agree with submission of the NDA with three months of available stability data?

***FDA Response:*** *Yes, provided that at least three stability data points are included in the stability data at the time of submission. This suggestion is made to ensure sufficient data for projection of shelf life during the review. The shelf life granted will be dependent on the quality and quantity of the data received at the time of submission. The application is expected to be complete at the time of submission. Additional stability data submitted during the review of the NDA may not necessarily be used to support the shelf life at the time of approval.*

**NONCLINICAL QUESTIONS**

***Nonclinical Question 1***

Based on existing pharmacokinetic data for each of the individual components, as well as a single-dose ocular uptake study in pigmented rabbits with the fixed combination, Alcon plans to conduct 2 additional studies to support the approval of brinzolamide 1%/ brimonidine 0.2% ophthalmic suspension. These are a toxicokinetic assessment of brinzolamide and brimonidine in a 9-month topical ocular toxicity study in pigmented rabbits and a multiple-dose (twice a day for 14 days) rabbit ocular uptake and tissue distribution study in pigmented rabbits. Does the FDA agree that these data are sufficient to characterize the pharmacokinetics of brinzolamide 1% / brimonidine 0.2% ophthalmic suspension?

***FDA Response:*** *The scope of the proposed pharmacokinetic studies appears to be sufficient; however, the adequacy of the data to support the NDA application will be evaluated upon review of the final study reports. The clinical formulation should be used for both studies. The rabbit ocular uptake and tissue distribution study should elucidate ocular exposure levels ( $C_{max}$  and AUC) as well as examine distribution and accumulation in ocular tissues including melanin-rich ocular structures (iris/ciliary and anterior retina/choroids).*

### ***Nonclinical Question 2***

Based on existing toxicology data for each of the individual components, as well as a 6-week topical ocular toxicity evaluation with the fixed combination, Alcon plans to conduct a 9-month topical ocular toxicity study with a 3-month interim evaluation in pigmented rabbits in support of the NDA. Does the FDA agree?

***FDA Response:*** *Agreed. However, as noted in the "Guidance for Industry: Nonclinical Safety Evaluation of Drug or Biologic Combinations" a bridging study of 3-months duration is sufficient to support a chronic indication for a new combination product. Thus the 9-month topical ocular toxicity study can be limited to 3 months. The clinical formulation should be used, and histopathology should extend to adjunct ocular tissues including the optic nerve. As specified in the same guidance, an embryo-fetal development study with the combination product should be conducted in support of the NDA application. Should the results of the nonclinical studies suggest safety concerns, or if issues arise in the clinic, further nonclinical studies may be required.*

***Additional FDA comment:*** *Please provide a formal justification submitted as an IND supporting document relating the reasons why an embryo-fetal development study with the combination product should not be required in support of the NDA application. The Agency will further evaluate this issue and the need for a combination study based on the information provided in the justification.*

## **CLINICAL QUESTIONS**

### ***Clinical Question 1***

Alcon proposes to conduct a single clinical pharmacokinetic study (C-10-010; Clinical Appendix B) to compare the systemic exposure of both brinzolamide and brimonidine in the fixed combination with their individual components (brinzolamide 1% and brimonidine 0.2%). No additional clinical pharmacokinetic studies are planned. The existing data on the absorption, distribution, metabolism, excretion, and special populations for brinzolamide and brimonidine following topical ocular administration will be used to support the NDA submission of brinzolamide 1% / brimonidine 0.2% ophthalmic suspension. Does the FDA agree that these data are sufficient?

***FDA Response:*** *Agree. Measurement of plasma and whole blood concentrations of brinzolamide is recommended if a more sensitive analytical method in plasma is available (with a lower limit of quantification less than 10 ng/mL) since the presence of a drug-drug interaction may not be readily apparent with whole blood concentrations of brinzolamide.*

***Additional FDA comment:*** *The Sponsor indicated a lower limit of quantification of 7.5 ng/mL was achieved in the past for detection of brinzolamide and its metabolite in plasma but*

*quantifiable concentrations in plasma were due to hemolysis of samples. The Division stated that a lower limit of quantification (LLOQ) of 7.5 ng/mL was not enough of an improvement from 10 ng/mL to quantify brinzolamide concentrations in plasma and efforts to lower the plasma LLOQ below 7.5 ng/mL for brinzolamide and its metabolite should be discussed in the NDA. The Sponsor clarified that the intent of the pharmacokinetic study was to evaluate a drug-drug interaction effect on the RBC saturation of brinzolamide. The Division expressed concern over whether a drug-drug interaction could be detected if complete RBC saturation is expected to occur during the 2-week PO loading dose phase. The Sponsor indicated RBC saturation following PO dosing is expected to decrease during the 13-week topical ocular dosing phase which would allow for evaluation of a drug-drug interaction. However, the Sponsor also proposed measuring plasma concentrations of brinzolamide in the event RBC saturation does not decrease with topical ocular dosing. The Division concurred with the Sponsor's rationale and plan.*

***Clinical Question 2***

Alcon proposes that the treatment duration for the 2 contribution of elements trials will be 3 months. Does the FDA agree?

***FDA Response:*** Agree. The clinical trials should demonstrate superiority of the combination product to each of the individual components, i.e. a clinically significant contribution of each individual component of the proposed combination drug product for the lowering of intraocular pressure (IOP).

***Clinical Question 3***

Alcon proposes to measure IOP at 8 AM, 10 AM, 3 PM and 5 PM at 2 Eligibility Visits and at 3 on-therapy visits (Week 2, Week 6, Month 3). Does the FDA agree that the time points and visits are appropriate?

***FDA Response:*** Yes.

***Additional FDA comment:*** Each timepoint should be measured and analyzed separately and compared to baseline.

***Clinical Question 4***

Alcon proposes to use mean IOP at Month 3 (8 AM, 10 AM, 3 PM and 5 PM) as the primary efficacy endpoint for both contribution of elements trials. Hypothesis tests will be performed using a repeated measures analysis of variance method. Treatment group comparisons at each of the study visits and times will be pair-wise tests based on the least squares means from the analysis of variance (ANOVA). The primary comparisons of interest are brinzolamide 1%/brimonidine 0.2% ophthalmic suspension vs. brinzolamide ophthalmic suspension, 1% and brinzolamide 1%/brimonidine 0.2% ophthalmic suspension vs. brimonidine ophthalmic solution, 2% at all Month 3 time points (8 AM, 10 AM, 3 PM and 5 PM). The remaining

comparisons at 8 AM, 10 AM, 3 PM and 5 PM for the Week 2 and Week 6 Visits will provide additional supportive efficacy. Primary inference will be based on the intent-to-treat data set. Last-observation-carried-forward (LOCF) will be used to impute missing data in the intent-to-treat analysis. Does the FDA agree?

***FDA Response: No.***

1. *A repeated measures analysis is not recommended.*
2. *The proposal does not address the difference needed to demonstrate clinical significance.*
3. *We cannot comment on the appropriateness of the proposed analysis of variance since the protocol did not provide sufficient details. We recommend that you provide details on the analysis method and specify the fixed effects, random effects, and the covariance structure for the IOP measurements at the multiple time points in the ANOVA model.*
4. *We recommend that you conduct sensitivity analyses using other imputation methods (e.g., worst observation carried forward, multiple imputations, etc.) for missing data.*
5. *We recommend excluding patients with central corneal thickness > 620 microns.*
6. *Randomization should include stratification for baseline factors which can significantly impact the outcome. Typically, in the reduction of intraocular pressure, the baseline intraocular pressure can influence the outcome.*
7. *We recommend measuring visual field (VF), pupil size, and cup to disc ratio (C/D) are recommended to be performed at baseline, months 3, 6, and 12. If a trial ends at 3 months it is acceptable to perform the measurements at baseline and 3 months.*
8. *Pupil size measurements are recommended to be recorded in 0.5 mm increments.*
9. *Central corneal thickness (pachymetry) is recommended to be measured at baseline.*
10. *An evaluation of patient comfort after the administration of the drug product is recommended to be completed. If topically administered, dosing of drops should be at least 30 minutes after use of any anesthetic agent or IOP measurement.*
11. *Endothelial cell count examinations are recommended to be performed at baseline and at the end of trial in at least one study.*
12. *To establish safety, it is recommended that approximately 500 or more subjects using the test drug product complete treatment with a concentration of the test drug product at least as high as proposed for marketing with a frequency at least as frequent as proposed for marketing. In addition, safety information from at least 100 patients treated for at least 6 months should be collected.*
13. *Only a synopsis for Protocols C-10-033 and C-10-039 are provided; additional comments will be made once the final protocols are submitted.*

**ISSUES REQUIRING FURTHER ACTION – None**

**ACTION ITEMS – Issue minutes within 30-days.**

IND 106,293  
Meeting Minutes

---

Lori Gorski, Meeting Recorder

---

Wiley Chambers, Meeting Chair

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

/s/  
-----

WILEY A CHAMBERS  
12/17/2010