

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**204251Orig1s000**

**OTHER REVIEW(S)**

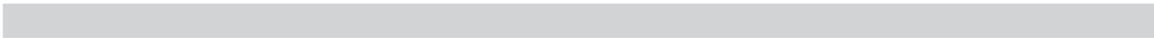
505(b)(2) ASSESSMENT

Application Information		
NDA # 204251	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: Simbrinza Established/Proper Name: brinzolamide 1%/brimonidine tartrate 0.2% Dosage Form: ophthalmic suspension Strengths:		
Applicant: Alcon Research, Inc.		
Date of Receipt: June 19, 2012		
PDUFA Goal Date: April 19, 2013	Action Goal Date (if different):	
Proposed Indication(s): Reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension		

GENERAL INFORMATION

- 1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?
- YES  NO

*If "YES" contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*



**INFORMATION PROVIDED VIA RELIANCE  
(LISTED DRUG OR LITERATURE)**

- 2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug or by reliance on published literature. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of referenced product)	Information provided (e.g., pharmacokinetic data, or specific sections of labeling)
Alphagan (brimonidine tartrate), NDA 20613-Allergan	Contraindications, Warnings & Precautions, Adverse Reactions, Drug Interactions, Use in Specific Populations, Overdosage, Description, Clinical Pharmacology, Non-Clinical Toxicology, Patient Counseling Information

\*each source of information should be listed on separate rows

- 3) Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific “bridge” to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)

*The application has been submitted as a 505(b)(2) application because the applicant (Alcon) does not have a right to reference some of the non-clinical studies used to support the Pregnancy, Nursing Mothers, and Carcinogenesis, Mutagenesis, Impairment of Fertility sections of the labeling. Alcon also does not have a right to reference some of the studies which support the labeling references to brimonidine ophthalmic solution. The drug product which is the subject of this application (Simbrinza (brinzolamide/brimonidine ophthalmic suspension) 1%/0.2%) is linked to the non-clinical studies by chemical analyses which confirm that brimonidine tartrate is a component of both Simbrinza and the oral drug product that was used in the non-clinical studies. The drug product used for the non-clinical studies is not Simbrinza, but is instead an oral product given to exaggerate the potential exposure of brimonidine. The use of this different oral product is necessary to exaggerate the potential exposure. The oral product used to exaggerate the potential exposure is the same as was used to exaggerate the exposure of the reference drug product in NDA 20-613. References to brimonidine ophthalmic solution in the labeling do not refer to Simbrinza, but instead refer to the reference drug product in NDA 20-613. They are included in the labeling of Simbrinza because the regulations require the inclusion of relevant Warnings/Precautions/Adverse Events associated with products in the same class as the drug product which is the subject of this application.*

**RELIANCE ON PUBLISHED LITERATURE**

4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved without the published literature)?

YES  NO   
*If "NO," proceed to question #5.*

(b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES  NO   
*If "NO," proceed to question #5.*  
*If "YES", list the listed drug(s) identified by name and answer question #4(c).*  
**Alphagan**

(c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES  NO

**RELIANCE ON LISTED DRUG(S)**

*Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.*

5) Regardless of whether the applicant has explicitly referenced the listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES  NO   
*If "NO," proceed to question #10.*

6) Name of listed drug(s) relied upon, and the NDA/ANDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Drug	NDA/ANDA #	Did applicant specify reliance on the product? (Y/N)
Brimonidine Tartrate (Alphagan)	NDA 20613	Yes

*Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been*

explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A  YES  NO

If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer "N/A".

If "NO", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 8) Were any of the listed drug(s) relied upon for this application:

a) Approved in a 505(b)(2) application?

YES  NO

**NOTE: Although the 356h form for NDA 20613 (brimonidine tartrate, 0.2%) lists NDA 20490 (brimonidine tartrate, 0.5%) as a reference (both products by Allergan), NDA 20613 was approved as an NME on September 6, 1996, before NDA 20490, approved March 13, 1997.**

If "YES", please list which drug(s).

Name of drug(s) approved in a 505(b)(2) application:

b) Approved by the DESI process?

YES  NO

If "YES", please list which drug(s).

Name of drug(s) approved via the DESI process:

c) Described in a monograph?

YES  NO

If "YES", please list which drug(s).

Name of drug(s) described in a monograph:

d) Discontinued from marketing?

YES  NO

If "YES", please list which drug(s) and answer question d) i. below.

If "NO", proceed to question #9.

Name of drug(s) discontinued from marketing: **Alphagan**

i) Were the products discontinued for reasons related to safety or effectiveness?

YES  NO

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

- 9) Describe the change from the listed drug(s) relied upon to support 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 capsule to solution").

**This application provides for a new combination of two previously approved products**

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

*The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered **YES to question #1**, proceed to question #12; if you answered **NO to question #1**, proceed to question #10 below.*

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

*(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)).*

*Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.*

YES  NO

*If "NO" to (a) proceed to question #11.  
If "YES" to (a), answer (b) and (c) then proceed to question #12.*

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

YES  NO

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

YES  NO

*If "YES" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.*

*If "NO" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

*(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.)*

*Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.*

YES  NO

*If "NO", proceed to question #12.*

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

YES  NO

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

YES  NO

*If "YES" and there are no additional pharmaceutical alternatives listed, proceed to question #12.*

*If "NO" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical alternative(s):

<b>PATENT CERTIFICATION/STATEMENTS</b>
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12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s): B

No patents listed  *proceed to question #14*

13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES  NO

*If "NO", list which patents (and which listed drugs) were not addressed by the applicant.*

Listed drug/Patent number(s):

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

No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)

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

21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

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

Patent number(s):

Expiry date(s):

21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*

21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*

21 CFR 314.50(i)(1)(ii): No relevant patents.

21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):

Method(s) of Use/Code(s):

15) Complete the following checklist **ONLY** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

(a) Patent number(s):

(b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?

YES  NO

*If "NO", please contact the applicant and request the signed certification.*

- (c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES  NO

*If "NO", please contact the applicant and request the documentation.*

- (d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s):

- (e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

*Note that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information **UNLESS** the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.*

YES  NO  Patent owner(s) consent(s) to an immediate effective date of approval

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/s/  
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JUDIT R MILSTEIN

04/19/2013

NDA 204251- 505(b)(2) assessment form

**FOOD AND DRUG ADMINISTRATION  
Center for Drug Evaluation and Research  
Office of Prescription Drug Promotion**

**\*\*\*Pre-decisional Agency Information\*\*\***

## Memorandum

**Date:** April 9, 2013

**To:** Judit Milstein, CPMS  
Division of Transplant and Ophthalmology Products (DTOP)  
Office of Antimicrobial Products (OAP)

**From:** Christine Corser, Regulatory Review Officer  
Office of Prescription Drug Promotion (OPDP)

**Subject:** **SIMBRINZA™ (brinzolamide/brimonidine tartrate)1%/0.2%**  
NDA #204251

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As requested in your consult dated August 21, 2012, OPDP has reviewed the draft PI for SIMBRINZA™ (brinzolamide/brimonidine tartrate)1%/0.2%.

OPDP's comments are based on the proposed, clean, substantially complete version of the PI obtained from the eRoom on April 8, 2013.  
([http://erom.fda.gov/eRoom/CDER1/CDERDivisionofSpecialPathogenandTransplantProductsNDA/0\\_37010](http://erom.fda.gov/eRoom/CDER1/CDERDivisionofSpecialPathogenandTransplantProductsNDA/0_37010))

Thank you for the opportunity to provide comments on this PI. If there are any questions, please contact me at 301-796-2653 or [Christine.corser@fda.hhs.gov](mailto:Christine.corser@fda.hhs.gov).

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/s/  
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CHRISTINE G CORSER  
04/09/2013

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology  
Office of Medication Error Prevention and Risk Management**

**Label, Labeling and Packaging Review**

Date: March 14, 2013

Reviewer: Jung Lee, RPh  
Division of Medication Error Prevention and Analysis

Team Leader: Jamie Wilkins Parker, PharmD  
Division of Medication Error Prevention and Analysis

Division Director: Carol Holquist, RPh  
Division of Medication Error Prevention and Analysis

Drug Name and Strength: Simbrinza (Brinzolamide and Brimonidine Tartrate  
Ophthalmic Suspension), 1% /0.2%

Application Type/Number: NDA 204251

Applicant: Alcon Research, Ltd

OSE RCM #: 2012-1539

\*\*\* This document contains proprietary and confidential information that should not be released to the public.\*\*\*

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## 1 INTRODUCTION

This review evaluates the proposed container label, carton, and insert labeling for Simbrinza (NDA 204251) for areas of vulnerability that could lead to medication errors.

### 1.1 REGULATORY HISTORY

On July 3, 2012, the Applicant submitted the application under NDA 204251.

### 1.2 PRODUCT INFORMATION

The following product information is provided in the July 3, 2012 submission.

- Active Ingredient: Brinzolamide and Brimonidine Tartrate
- Indication of Use: Reduction of intraocular pressure (IOP) for patients with open-angle glaucoma (OAG) and/or ocular hypertension (OHT)
- Route of Administration: Ophthalmic
- Dosage Form: Ophthalmic Suspension
- Strength: 1%/0.2%
- Dose and Frequency: One drop in affected eye(s) 3 times a day
- How Supplied: (b)(4) 8 mL in 10 mL LDPE DROP-TAINER bottle with (b)(4) cap
- Storage: Store at 2°C to 25°C (36°F to 77°F)
- Container and Closure Systems: Sterile opaque 10 mL white LDPE plastic DROP-TAINER bottles and natural tips with (b)(4) polypropylene caps.

○

(b)(4)

### 1.3 LABELS AND LABELING

Using the principles of human factors and Failure Mode and Effects Analysis,<sup>1</sup> along with post marketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Container Labels submitted February 26, 2013 (Appendix B)
- Carton Labeling submitted February 26, 2013 (Appendix C)
- Insert Labeling submitted February 26, 2013

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<sup>1</sup> Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

## 2 DEFICIENCIES

(b) (4)

(b) (4) The Division stated “The AAO doesn't currently have a cap color designated for this particular drug combination; in the absence of a designated cap color, the cap should be white. The stability studies were all performed with white caps so there should be no problem.” A recommendation will be made to the Applicant to change the color of the cap to white, a color that does not overlap with the existing cap color coding system for topical ocular medications.

## 3 RECOMMENDATIONS

Based on this review, DMEPA recommends the following be implemented prior to approval of this NDA:

### 3.1 COMMENTS TO THE REVIEW DIVISION

1. As previously discussed with the review Division, we request the cap color be revised to white, (b) (4)

### 3.2 COMMENTS TO THE APPLICANT

- A. Container Label ( (b) (4) 8 mL Trade Size)
  1. Revise the presentation of the proprietary name from all upper case letters “SIMBRINZA” to title case “Simbrinza” to improve readability. Words set in title case form recognizable shapes, making them easier to read.
  2. Replace the “ / ” (forward slash) separating the two active ingredients in the established name with the word “and” so it reads as follows: brinzolamide and brimonidine tartrate ophthalmic suspension.
  3. Decrease the prominence of the manufacturer’s name on the principal display panel by debolding.
  4. Increase the prominence of the strength statement as this important information currently lacks prominence. The company name appears larger than the strength. The name and strength should have the greatest prominence on the label.
  5. If space permits, include the statement “Shake Well Before Use” on the side panel.

- B. Carton Labeling ( [REDACTED] <sup>(b) (4)</sup> 8 mL Trade Size)
1. See comments A1 to A3.
  2. Increase the amount of white space between the established name and the strength statement for increased readability and clarity.
  3. Relocate the route of administration statement “For Topical Ophthalmic Use Only” to the principal display panel to appear just below the established name and strength.

If you have further questions or need clarifications, please contact Karen Townsend, project manager, at 301-796-5413.

## APPENDICES

### APPENDIX A. DATABASE DESCRIPTIONS

#### Adverse Event Reporting System (AERS)

The Adverse Event Reporting System (AERS) is a computerized information database designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The FDA uses AERS to monitor adverse events and medication errors that might occur with these marketed products. The structure of AERS complies with the international safety reporting guidance ([ICH E2B](#)) issued by the International Conference on Harmonisation. Adverse events in AERS are coded to terms in the Medical Dictionary for Regulatory Activities terminology (MedDRA).

AERS data do have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive all adverse event reports that occur with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, AERS cannot be used to calculate the incidence of an adverse event in the U.S. population.

(b) (4)

2 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS)  
immediately following this page.

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/s/  
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JUNG E LEE  
03/14/2013

JAMIE C WILKINS PARKER  
03/14/2013

CAROL A HOLQUIST  
03/14/2013

MEMORANDUM

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

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**CLINICAL INSPECTION SUMMARY**

DATE: February 22, 2013

TO: Judit Milstein, Supervisory Consumer Safety Officer  
Lucious Lin, M.D., M.P.H, Medical Officer  
William M. Boyd, Medical Team leader  
Division of Transplant and Ophthalmology Products

FROM: Kassa Ayalew, M.D., Medical Officer  
Good Clinical Practice Assessment Branch  
Division of Good Clinical Practice Compliance  
Office of Scientific Investigations

THROUGH: Susan Leibenhaut, M.D.  
Acting Team Leader  
Good Clinical Practice Assessment Branch  
Division of Good Clinical Practice Compliance  
Office of Scientific Investigations

Susan Thompson, M.D.  
Acting Branch Chief  
Good Clinical Practice Assessment Branch  
Division of Good Clinical Practice Compliance  
Office of Scientific Investigators

SUBJECT: Evaluation of Clinical Inspections

NDA: 204251

APPLICANT: Alcon Research, Ltd.

DRUG: Simbrinza (brinzolamide 1%/brimonidine tartrate 0.2% ophthalmic suspension)

NME: No

INDICATION: reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension

THERAPEUTIC CLASSIFICATION: Standard

CONSULTATION REQUEST DATE: October 16, 2012

PDUFA: April 19, 2013

Action Goal Date: March 19, 2013

Inspection Summary Goal Date: March 19, 2013

## I. BACKGROUND:

Alcon Research Ltd. submitted NDA 204251 for a new fixed-combination ophthalmic suspension of Brinzolamide 1% and Brimonidine Tartrate 0.2% pursuant to 505(b)(1) of the Federal Food, Drug and Cosmetic Act and 21 CFR 314.50. The proposed indication is reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension. Brinzolamide 1% is a carbonic anhydrase inhibitor and Brimonidine Tartrate 0.2% is an alpha 2-adrenergic agonist, and these individual components are currently approved products for the indication. The product is dosed three times a day and is being developed as a non  $\beta$ -blocker containing topical ocular therapy for the reduction of elevated intraocular pressure (IOP) in patients with open angle glaucoma or ocular hypertension. Both Brinzolamide and Brimonidine decrease elevated IOP by reducing aqueous humor secretion, but do so by different mechanisms of action. The sponsor claims that treatment of open angle glaucoma or ocular hypertension in patients with Brinzolamide 1%/ Brimonidine tartrate 0.2% fixed dose combination provides IOP-lowering efficacy which may be superior to either individual agent dosed as mono-therapy without any additional safety risk as compared to either of the individual components

The Office of Scientific Investigation received a consult from Division of Transplant and Ophthalmology Products to conduct clinical inspections of the following two identical studies:

**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

**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

The studies were multicenter, randomized, double-masked, parallel-group, active-controlled studies intended to evaluate the safety and efficacy of a fixed combination of Brinzolamide/Brimonidine in lowering Intraocular Pressure (IOP) relative to each of its

individual active components in patients with open-angle glaucoma and/or ocular hypertension. The primary efficacy endpoint was the mean IOP at each of the assessment time points (8 AM, + 2 h, + 7 h, and + 9 h) at Month 3. The superiority of Brinzolamide/Brimonidine to each of its individual active components (Brinzolamide and Brimonidine) with respect to treatment group differences in mean IOP was determined using pairwise tests at each time point. Approximately 1350 subjects in the USA were to be enrolled in the two studies.

One site from each study was chosen for inspection based on enrollment, number of INDs in the OSI database, and previous inspectional history.

## II. RESULTS (by Site):

Name of CI	Protocol # /Site #/ # of Subjects Enrolled:	Inspection Date	Classification
<b>George C. Thorne, M.D.</b> Eye Physicians of Austin 5011 Burnet Road Austin, TX 78756	Study C-10-039/2353/ n=27	December 4 to 7 , 2012	NAI
<b>Eugene B. McLaurin, M.D.</b> Total Eye Care, PA 6060 Primacy Parkway Suite 200 Memphis, TN 38119	Study C-10-033/4011/ n=52	November 26 to 29, 2012,	NAI

### Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data unreliable.

Pending = Preliminary classification based on information in 483 or preliminary communication with the field;  
EIR has not been received from the field and complete review of EIR is pending.

### 1. **George C. Thorne, M.D.**

Eye Physicians of Austin  
5011 Burnet Road  
Austin, TX 78756

#### a. **What was inspected?**

This inspection was performed a data audit for Protocol # C-10-039. There are 17 INDs associated with the inspected entity in CDER's database, and the CI had no prior inspection.

There were a total of 27 subjects screened, 19 of those completed the study, and 8 did not complete the study. There were no minors or vulnerable subjects screened or enrolled into the study.

At this site, a total of 27 study subjects were screened for Protocol # Study C-10-039. A total of 19 subjects completed the study. An in depth audit of the study records for all subjects were conducted. There was no evidence of under reporting of adverse events. The primary efficacy endpoint data was verifiable. There were no SAE's recorded at this site.

Records reviewed included, but were not limited to, source documents, protocol specified blinding/randomization procedures, inclusion/exclusion criteria, adverse events, primary efficacy endpoints, protocol deviations, concomitant therapies, and test article accountability. In addition, IRB correspondence, monitoring logs and correspondence, and financial disclosure documentation were reviewed.

**b. General observations/commentary:**

A Form FDA 483, Inspectional Observations, was issued for failure to conduct the study in accordance with the signed statement of investigator and investigational plan [21 CFR 312.60] because, for a single subject (Subject (b) (6)/017/2209), the informed consent document was not dated by the subject or the subject's legally authorized representative. The clinical investigator wrote the dates for the subject at the time of consent.

**c. Assessment of data integrity:**

Based on the isolated nature of the violation cited on the Form FDA 483, this inspection is downgraded to NAI. The data derived from Dr. Thorne's site are considered reliable and can be used in support of the indication.

**2. Eugene B. McLaurin, M.D.**

Total Eye Care, PA  
6060 Primacy Parkway Suite 200  
Memphis, TN 38119

**a. What was inspected?**

This inspection was performed a data audit for Protocol # C-10-033. There are 18 INDs associated with the inspected entity in CDER's database, and the CI had no prior inspection.

At this site, a total of 52 study subjects were screened and enrolled for Protocol # C-10-033. A total of 42 subjects completed the study. There were no limitations to the inspection. An in depth audit of the study records for 52 subjects was conducted. The inspection included reviews of the following items: 1) entry criteria, 2) diagnosis of target disease, 3) efficacy variables, and 4) adequacy of adverse experience reporting. In addition, drug accountability records, Informed Consent Documents, IRB approval and dates, and sponsor monitoring records were reviewed.

**b. General observations/commentary:**

The study appears to have been executed appropriately at this site. No regulatory violations were noted and a Form FDA 483 was not issued.

**c. Assessment of data integrity:**

The study appears to have been conducted adequately, and the data generated from Dr. McLaurin's site appear acceptable in support of the indication.

**III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS**

Two clinical investigator sites were inspected for this application. The data derived from both inspected sites are considered reliable. The classification of the Clinical Investigator inspection of Dr. Thorne and Dr McLaurin is No Official Action Indicated (NAI).

*{See appended electronic signature page}*

Kassa Ayalew, M.D.  
Good Clinical Practice Assessment Branch  
Division of Good Clinical Practice Compliance  
Office of Scientific Investigations

**CONCURRENCE:**

*{See appended electronic signature page}*

Susan Leibenhaut, M.D.  
Acting Team Leader  
Good Clinical Practice Assessment Branch  
Division of Good Clinical Practice Compliance  
Office of Scientific Investigations

*{See appended electronic signature page}*

Susan Thompson, M.D.  
Acting Branch Chief  
Good Clinical Practice Assessment Branch  
Division of Good Clinical Practice Compliance  
Office of Scientific Investigations

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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KASSA AYALEW  
02/22/2013

SUSAN LEIBENHAUT  
02/22/2013

SUSAN D THOMPSON  
02/22/2013

## DSI CONSULT: Request for Clinical Inspections

**Date:** October 16, 2012

**To:** Tejashri Purohit-Sheth, M.D., Branch Chief, GCP 2  
Jean M. Mulinde, M.D., Acting Team Leader, GCP 2  
Kassa Ayalew, M.D. Medical Officer  
Division of Scientific Investigation  
Division of Scientific Investigations, HFD-45  
Office of Compliance/CDER

**Through:** Lucious Lin, MD, MPH, Medical Officer, 301-796-0749  
Division of Transplant and Ophthalmology Products

**From:** Judit Milstein, Sup Consumer Safety Officer, 301-796-0763  
Division of Transplant and Ophthalmology Products

**Subject:** Request for Clinical Site Inspections

### I. General Information

Application#: NDA 204251  
Applicant/ Applicant contact information: Alcon Research, Ltd  
6201 Freeway, Mail code R3-52  
Fort Worth, TX 76134-2099  
Contact: Katherine Rath, Assistant Director  
Regulatory Affairs  
(817) 302-5912

Drug: Simbrinza (brinzolamide 1%/brimonidine tartrate 0.2% ophthalmic suspension)

NME: No

Review Priority: No

Study Population includes < 17 years of age: No

Is this for Pediatric Exclusivity: No

Proposed Indication: reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension

PDUFA: April 19, 2013

Action Goal Date: March 19, 2013

Inspection Summary Goal Date: February 19, 2013

**II. Protocol/Site Identification**

<b>Site # (Name, Address, Phone number, email, fax#)</b>	<b>Protocol ID</b>	<b>Number of Subjects Randomized</b>	<b>Indication</b>
DSI Choice	C-10-033	660	reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension
DSI Choice	C-10-039	690	reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension

**III. Site Selection/Rationale**

The clinical portion of the application has been preliminarily reviewed, and no issues have been identified to date to suggest a problem with data integrity.

An inspection is requested for at least one site for each of these clinical trials only as your resources permit.

Note that the highest enrollers in Study C-10-033 are: Eugene B. McLaurin, MD (44), Kenneth Sall, MD (41), Harvey B. DuBiner, MD (29), and Steven H. Rauchman, MD (29).

Note that the highest enrollers in Study C-10-039 are: David Wirta, MD (30), George Thorne, MD (25) and Howard Schenker, MD (23).

**Domestic Inspections:**

Reasons for inspections (please check all that apply):

- Enrollment of large numbers of study subjects
- High treatment responders (specify):
- Significant primary efficacy results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
- Other (specify): Routine Inspections

**International Inspections:**

Reasons for inspections (please check all that apply):

- There are insufficient domestic data
- Only foreign data are submitted to support an application
- Domestic and foreign data show conflicting results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.
- Other (specify) (Examples include: Enrollment of large numbers of study subjects and site specific protocol violations. This would be the first approval of this new drug and most of the limited experience with this drug has been at foreign sites, it would be desirable to include one foreign site in the DSI inspections to verify the quality of conduct of the study).

**Goal Date for Completion:**

We request that the inspections be performed and that the Inspection Summary Results be provided by February 19, 2013. We intend to issue an action letter on this application by March 19, 2013. The PDUFA due date for this application is **April 19, 2013**.

Should you require any additional information, please contact Judit Milstein at 301-796-0763 or Lucious Lim, MD, MPH at 301-796-0749.

**Additional Information:**

This is an electronic NDA. The List and Description of Investigators for the previously identified studies are provided below.

**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**

List of Investigators C-10-033			
Site	Investigator	Address	Subjects Randomized
1660	<b>Bruce S. Altman, MD</b>	Danbury Eye Physicians & Surgeons PC 69 Sand Pit Rd, Suite 101 Danbury, CT 06810	4
4601	<b>George Arzeno, MD</b>	100 Paseo San Pablo Edif. Arturo Cadilla, Suite 502 Bayamon, PR 00961	5
4421	<b>Kent Bashford, DO</b>	Eye Center of Northern Colorado, PC 1725 East Prospect Road Fort Collins, CO 80525	7
5770	<b>Donald W. Bennett, OD, MD</b>	Kentuckiana Institute for Eye Research dba Bennett and Bloom Eye Centers Dupont Professional Towers 4010 Dupont Circle, Suite 380	1

<b>List of Investigators C-10-033</b>			
<b>Site</b>	<b>Investigator</b>	<b>Address</b>	<b>Subjects Randomized</b>
		Louisville, KY 40207	
5476	<b>Mark Bergmann, MD</b>	Eye Care Assoc Of Greater Cincinnati Inc 2859 Boudinot Ave, Suite 301 Cincinnati, OH 45238	0
5443	<b>Ettaleah Bluestein, MD</b>	Bluestein Custom Vision 2145 Henry Tecklenburg Dr. St. Francis Medical Plaza, Suite 100 Charleston, SC 29414	4
4570	<b>J. Brent Bond, MD</b>	Wake Forest University Eye Center Janeway Tower, 6th Floor Medical Center Blvd Winston-Salem 27157	3
5239	<b>James D. Boyce, MD</b>	Orange County Ophthalmology Medical 12665 Garden Grove Blvd, Suite 401 Garden Grove, CA 92843	2
3631	<b>James David Branch, MD</b>	James David Branch, MD 224 Town Run Lane Winston-Salem, NC 27101	20
3910	<b>Richard Chace, MD</b>	Eyesight Ophthalmic Services, PA 155 Borthwick Avenue, Suite 200 East Portsmouth, NH 03801	6
2346	<b>Doug Dehnig, MD</b>	Discover Vision Center 4741 S. Cochise Drive Independence, MO 64055	5
5303	<b>El-Roy Dixon, MD</b>	Dixon Eye Care 806 N. Jefferson St. Albany, GA 31701	18
1927	<b>Harvey B. DuBiner, MD</b>	Eye Care Centers Management Clayton Eye Center 1000 Corporate Center Dr., Suites 100 & 120 Morrow, GA 31701	29
4032	<b>Christopher Engelman, MD</b>	Spectrum Eye Physicians 431 Monterey Ave., Suite 3 Los Gatos, CA 95030	5
5758	<b>Raymond Fong, MD</b>	Raymond Fong, MD, PC 109 Lafayette St., 4 <sup>th</sup> Floor New York, NY 10013	3
5289	<b>L. Wayne Freeman, MD</b>	The Health Care Center 1661 Golden Rain Road Seal Beach, CA 90740	5
5459	<b>Joseph P. Gira, MD</b>	Ophthalmology Consultants, Ltd 12990 Manchester Road, Suite 201 Des Peres, MO 63131	9
5489	<b>Damien F. Goldberg MD</b>	Wolstan & Gidbery Eye Associates 23600 Telo Ave., Suite 100 Torrance, CA 90505	10
5593	<b>Thomas Graul, MD</b>	Eye Surgical Associates 1710 South 70th St. Lincoln, NE 68506	11

<b>List of Investigators C-10-033</b>			
<b>Site</b>	<b>Investigator</b>	<b>Address</b>	<b>Subjects Randomized</b>
5582	<b>Brennan P. Greene, MD</b>	The Eye Care Institute 1536 Story Avenue Louisville, KY 40206	4
5480	<b>William L. Haynes, MD</b>	Asheville Eye Associates 8 Medical Park Drive Asheville, NC 28803	8
0983	<b>John Charles Henry, MD</b>	Little Rock Eye Clinic 9800 Lile Drive, Suite 400 Little Rock, AR 72205	4
5651	<b>Brian J. Jacobs, MD</b>	North Shore Glaucoma Center 1800 Hollister Drive, Suite 205 Libertyville, IL 6004	0
1159	<b>Gary Jerkins, MD</b>	Nashville Vision Associates 4306 Harding Rd, Suite 202 Nashville, TN 37205	23
0962	<b>Martin B. Kaback, MD</b>	Glaucoma Consultants Of The Capital Region 1240 New Scotland Road, Suite 201 Slingerlands, NY 12159	4
3731	<b>Gregory J. Katz, MD</b>	Huron Ophthalmology, PC 5477 West Clark Road Ypsilanti, MI 48197	16
6229	<b>Lawrence B. Katzen, MD</b>	Katzen Eye Care & Laser Center 901 North Congress Avenue, #104-B Boynton Beach, FL 33426	3
3974	<b>Alexander R. Kent, MD</b>	Palmetto Research LLC 125 Doughty St., Suite 330 Charleston, SC 29403	9
6102	<b>Charles Kirby, MD</b>	Chattanooga Eye Institute, P.C. 5715 Cornelison Rd, Bldg. #6600 Charleston, TN 37411	4
3678	<b>Jeffrey R. Lozier, MD</b>	Arch Health Partners 15611 Pomerado Road, Suite 400 Poway, CA 92604	18
2029	<b>Jonathan L. Macy, MD</b>	Macy Eye Center 8635 W. 3rd Street, Suite 360W Los Angeles, CA 90048	7
6228	<b>Hylton Mayer, MD</b>	Eye Doctors of Washington 2 Wisconsin Circle, Suite 200 Chevy Chase, MD	1
4011	<b>Eugene B. McLaurin, MD</b>	Total Eye Care,PA 6060 Primacy Parkway, Suite 200 Memphis, TN 38119	44
1473	<b>Thomas Mundorf, MD</b>	Mundorf Eye Center 1718 E 4th St., Suite 703 Charlotte, NC 28204	17
5769	<b>Matthew Nutaitis, MD</b>	MUSC Storm Eye Institute 167 Ashley Ave., MSC676 Charleston, SC 29425	2
5333	<b>Constance Okeke, MD</b>	Virginia Eye Consultants	3

<b>List of Investigators C-10-033</b>			
<b>Site</b>	<b>Investigator</b>	<b>Address</b>	<b>Subjects Randomized</b>
		241 Corporate Blvd. Norfolk, VA 23502	
0750	<b>Kenneth W. Olander, MD, PhD</b>	University Eye Surgeons 622 Smithview Drive Maryville, TN 37803	16
6039	<b>Mina Pantcheva, MD</b>	Rocky Mountain Lions Eye Inst. 1675 Aurora Court, Mailstop F-731 Aurora, CO 80045	5
3627	<b>James H. Peace, MD</b>	United Medical Research Institute 431-433 North Prairie Avenue Inglewood, CA 90301	15
3720	<b>Bernard R. Perez, MD</b>	International Eye Center 4506 Wishart Place Tampa, FL 33603	3
5176	<b>Scott L. Portnoy, MD</b>	Siegel and Portnoy Eyecare Associates 2026 East Carson St. Pittsburg, PA 15203	5
4146	<b>Richard Quinones, MD</b>	Arbor Center for Eye Care 2640 West 183rd St. Homewood, IL 60430	6
5180	<b>Steven H. Rauchman, MD</b>	North Valley Eye Medical Group, Inc. 11550 Indian Hills Rd, Suite 341 Mission Hills, CA 91345	29
2448	<b>Ned M. Reinstein, MD</b>	Reinstein Eye Associates, PC 7171 South Yale, Suite 101 Tulsa, OK 74136	8
6366	<b>Robert F. Rothman, MD, FACS</b>	Eye Care Ophthalmology, PC 4212 Hempstead Turnpike Bethpage, NY 11714	0
1725	<b>Jay M. Rubin, MD</b>	Eye Clinics of South Texas 999 East Basse Rd., Suite 128-B San Antonio, TX 78209	4
1806	<b>Kenneth Sall, MD</b>	Sall Research Medical Center 11423 187 <sup>th</sup> St., Suite 200 Artersia, CA 90701	41
4347	<b>John R. Samples, MD</b>	Glaucoma Consultants of Colorado dba Specialty Eye Care 11960 Lioness Way, Suite 190 Parker, CO 80134	3
0731	<b>Elizabeth D. Sharpe, MD</b>	Glaucoma Consultants & Center for Eye Research, PA 721 Longpoint Road, Suite 407 Mt. Pleasant, SC 29464	21
3346	<b>Phillip Lee Shettle, DO</b>	Shettle Eye Center 670 Clearwater-Largo Rd. Largo, FL 33770	18
1892	<b>Shannon Smith, MD</b>	Cataract, Glaucoma & Retina Consultants of East Texas 3302 N.E. Stallings Dr.	24

<b>List of Investigators C-10-033</b>			
<b>Site</b>	<b>Investigator</b>	<b>Address</b>	<b>Subjects Randomized</b>
		Nacogdoches, TX 75965	
6160	<b>Stacy R. Smith, MD</b>	4568 S. Highland Dr., Suite 160 Salt Lake City, UT 84117	12
2454	<b>Alfred M. Solish, MD</b>	Southern California Glaucoma Consultants 630 S Raymond Ave, Suite 230 Pasadena, CA 91105	1
3851	<b>Emil Stein, MD</b>	Nevada Eye Care Professionals 2090 E. Flamingo Rd., Suite 100 Las Vegas, NV 89119	17
2631	<b>W. Colby Stewart, MD</b>	Houston Eye Associates 2855 Gramercy Street Houston, TX 77025	8
3962	<b>Richard Sturm, MD</b>	Ophthalmic Consultants of Long Island 360 Merrick Rd, 3rd Floor Lynbrook, NY 11563	23
2128	<b>Gregory M. Sulkowski, MD</b>	Taustine Eye Center 1169 Easter Parkway, Suite 3427 Louisville, KY 40217	9
3993	<b>James Sutton, MD</b>	Mississippi Eye Associates 3631 Bienville Blvd. Ocean Spring, MS 39567	4
6339	<b>Matthew J. Swanic, MD</b>	AdvanceMed Clinical Research Eye Care Associates of Nevada 501 S. Rose St., Suite 150 Las Vegas, NV 89106	3
4338	<b>Thomas Tayeri, MD</b>	Palo Alto Eye Group 1805 El Camino Real, Suite 100 Palo Alto, CA 94306	2
3665	<b>Jean H. Tibbetts, MD</b>	Eastern Maine Medical Center Focus Eye Care of Maine 417 State St., Suite 230 Bangor, ME 04401	3
5468	<b>Farrell C. Tyson, MD</b>	Cape Coral Eye Center 3120 Del Prado Blvd. Cape Coral, FL 33904	12
4734	<b>Steven D. Vold, MD</b>	Boozman Hof Regional Eye Center 3737 W. Walnut St. Rogers, AR 72756	?
5397	<b>Jay Wallshein, MD</b>	Palm Beach Eye Center 5057 S. Congress Ave., #403 Atlantis, FL 33461	7
0394	<b>Mark Weiss, MD</b>	Mark Weiss, MD, Inc. 1717 S. Utica, Suite 107 Tulsa, OK 74104	25
6239	<b>Peter Wollan, MD</b>	Hill Country Eye Center 12171 W. Parmer Ln, Suite 201 Cedar Park, TX 78613	11
4194	<b>Todd F. Woodruff, MD</b>	The Glaucoma Center One Park West Blvd., Suite 310	11

<b>List of Investigators C-10-033</b>			
<b>Site</b>	<b>Investigator</b>	<b>Address</b>	<b>Subjects Randomized</b>
		Akron, OH 44320	

**C-10-039: A Three Month, Randomized, Double-Masked, Parallel-Group Study with a Planned Three-Month Safety Extension of the 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**

<b>List of Investigators C-10-039</b>			
<b>Site</b>	<b>Investigator</b>	<b>Address</b>	<b>Subjects Randomized</b>
4798	<b>Marc A Abrams, MD, PhD.</b>	Abrams Eye Center 2322 East 22nd St., Suite 102 Cleveland, OH 44115	4
6095	<b>Ahmad Amir, MD</b>	Pacific Eye 628 California Blvd #D San Luis Obispo, CA 93401	13
6100	<b>Guy J. Angella, MD</b>	Eye Surgery Associates 603 North Flamingo Road, Suite 250 Pembroke Pines, FL 33028	9
2434	<b>Jason Bacharach, MD</b>	North Bay Eye Associates 104 Lynch Creek Way, Suite 12 Petaluma, CA 94954	11
2195	<b>Howard Barnebey, MD</b>	Specialty Eyecare Centre 1920 116th Avenue NE Bellevue, Washington 98004	17
4404	<b>Janet A Betchkal, MD</b>	Gilbert Cataract Center 3 Shircliff Way Ste 134 Jacksonville, FL 32204	2
1946	<b>Leonard R. Cacioppo, MD</b>	Db: Hernando Eye Institute 14543 Cortez Blvd Brooksville, FL 34613	10
3712	<b>Williams C Christie, MD</b>	Scott & Christie and Associates, PC 1101 Freeport Road Pittsburgh, PA 15238	12
6243	<b>James P. Cornetet, MD</b>	Billings Clinic Research Center 1045 North 30th St. Billings, Montana 59101	1
4455	<b>Frank Cotter, MD</b>	Vistar Eye Center 707 S Jefferson St. Roanoke, VA 57149	15
3349	<b>Andrew J Cottingham, Jr., MD</b>	Texas Quest Medical Research, LLC 15900 La Cantera Parkway, Suite 19205 San Antonio, TX 7825	14
4189	<b>Charles J Crane, MD</b>	Northern New Jersey Eye Institute, PA	12

<b>List of Investigators C-10-039</b>			
<b>Site</b>	<b>Investigator</b>	<b>Address</b>	<b>Subjects Randomized</b>
		71 Second St. South Orange, NJ 07079	
2348	<b>Douglas Day, MD</b>	Omni Eye Services 5505 Peachtree-Dunwoody Road, Suite 300 Atlanta, GA 30342	10
6255	<b>Steven Day, MD</b>	Spokane Eye Clinical Research, PLLC 427 South Bernard Spokane, Washington 99204	4
1931	<b>Monte S Dirks, MD</b>	Black Hills Regional Eye Institute 2800 3rd St. Rapid City, SD 57701	11
3785	<b>Efraim Duzman, MD</b>	Lakeside Vision Center 4605 Barranca Pkwy, Suite 100 Irvine, CA 92604	6
2564	<b>Robert M Feldman, MD</b>	Robert Cizik Eye Clinic 6400 Fannin St., Suite 1800 Houston, TX	2
5636	<b>Mark Feldman, MD</b>	Fort Lauderdale Eye Institute 850 South Pine Island Road, Suite A 100 Plantation, FL 33324	9
5465	<b>Asra S. Firozvi, MD</b>	North Carolina Eye, Ear, Nose & Throat 4102 N Roxboro Road Durham, NC 27704	12
5145	<b>Williams J. Flynn, MD, OD</b>	R and R Eye Research, LLC 5430 Fredericksburg Road, Suite 100 San Antonio, TX 78229	14
2137	<b>Ronald Frenkel, MD</b>	East Florida Eye Institute 509 Southeast Riverside Dr., Ste 302 Stuart, FL 34994	12
1930	<b>Robert S. Friedman, MD</b>	The Eye Associates of Manatee, LLP 2111 Bee Ridge Road Sarasota, FL 34239	7
3377	<b>David Godfrey, MD</b>	Glaucoma Associates of Texas 10740 N Central Expressway, Suite 300 Dallas, TX 75231	1
4364	<b>Frank J. Grady, MD, PhD</b>	Frank J. Grady, MD, Association- Brazosport Eye Clinic 103 Parking Way St. Lake Jackson, TX 77566	14
6180	<b>Wade A. Graham, MD</b>	Thurmond Eye Associates, PA 1519 E 6th St. Weslaco, TX 78596	5
4567	<b>Robert F. Haverly, MD</b>	Laser Eye Surgery of Erie 311 West 24th Street, Suite 401 Erie, PA 16502	19
6232	<b>Joseph E. Humble, MD</b>	Eye Associates of Northeast Louisiana dba Haik Humble Eye Center 1804 North 7th St. West Monroe, LA 71291	15

<b>List of Investigators C-10-039</b>			
<b>Site</b>	<b>Investigator</b>	<b>Address</b>	<b>Subjects Randomized</b>
5404	<b>Michael Jacobs, MD</b>	Athens Eye Associates 1080 Vend Dr., Suite 100 Bogart, GA 30622	9
2449	<b>Barry Katzman, MD</b>	West Coast Eye Care Associates 6945 El Cajon Blvd San Diego, CA 92115	15
4247	<b>Dawnielle Kerner, MD</b>	The Glaucoma & Laser Center 160 Kingsley Lane, Suite 300 Norfolk, VA 23505	4
5304	<b>Karen L. Klugo, MD</b>	Eye Care Associates of Greater Cincinnati, Inc 5240 E. Galbraith Road, Suite B Cincinnati, OH 45236	15
3991	<b>Alexander Kostick, MD</b>	Atlantic Eye Center 3 Pine Cone Dr., Suite 104 Palm Coast, FL 32137	7
3112	<b>Bradley Kwapiszeski, MD</b>	Heart of America Eye Care, PA 8901 West 74th St., Suite 281 Shawnee Mission, KS 66204	12
5515	<b>John M. Lim, MD</b>	Houston Eye Associates 2855 Gramercy St. Houston, TX 77025	7
3975	<b>Christopher Lin, MD</b>	Shasta Eye Medical Group, Inc 3190 Churn Creek Road Redding, CA 96002	11
4780	<b>Jodi Ian Luchs, MD</b>	South Shore Eye Care, LLP 2185 Wantagh Avenue Wantagh, NY 11793	14
4824	<b>Ranjan P. Malhorta, MD</b>	Ophthalmology Associates 12990 Manchester Road, Suite 200 St. Louis, MO 63131	7
3830	<b>Cynthia Mattox, MD</b>	New England Eye Center at Tufts Medical Center 800 Washington St., Box 450 Boston, MA 02111	1
5387	<b>Donald McCormick, MD</b>	Boulder Medical Center PC 2750 Broadway Boulder, CO 80304	11
5583	<b>Ryan McKinnon, MD</b>	Saltzer Medical Group, PA 215 E Hawaii Avenue Nampa, ID 83686	11
2421	<b>Matthew G. McMenemy, MD</b>	Lone Star Eye Care 3515 Town Center Blvd South Sugarland, TX 77479	21
6099	<b>John L. Michaelos, MD</b>	St. Michael' s Eye & Laser Institute 1018 West Bay Dr. Largo, FL 33770	13
3722	<b>George A. Moninger, MD</b>	Botherman & Moninger, LLP 10 Medical Parkway, Plaza 3, Suite 102 Dallas, TX 75234-7840	6

<b>List of Investigators C-10-039</b>			
<b>Site</b>	<b>Investigator</b>	<b>Address</b>	<b>Subjects Randomized</b>
2576	<b>Martin W. Mizener, MD</b>	Midwest Eye Care PC 4353 Dodge St. Omaha, NE 68131	11
6159	<b>Quang H. Nguyen, MD</b>	Scripps Clinic 10666 North Torrey Pines Road, MS 214 La Jolla, CA 92037	11
1011	<b>Katherine Isabel Ochsner, MD</b>	Eye Associates of Wilmington 1729 New Hanover Medical Park Dr. Wilmington, NC 28403	4
5220	<b>Scott Petermann, MD</b>	South Georgia Eye Partners, PC 4380 Kings Way Valdosta, GA 31602	6
3967	<b>Jody Piltz-Seymour, MD</b>	Glaucoma Care Center, PC 100 Church Road Ardmore, PA 19003	8
6242	<b>Omar Piovanetti, MD</b>	Centro Oftalmologico Metropolitano 1250 JT Pinero Avenue San Juan, PR 00921	3
3132	<b>Eugene E. Protzko, MD</b>	Seidenberg Protzko Eye Associates 2023 Pulaski Hwy Havre de Grace, MD 21078	10
3362	<b>Anthony Realini, MD, Ph.D</b>	West Virginia University Eye Institute 1 Stadium Dr., Box 9193 Morgantown, WV 26506	5
5541	<b>Lawrence Roel, MD, PhD</b>	Eastside Eye Center 735 East Main Street Spartenburg, SC 29302	17
1393	<b>Michael H. Rotberg, MD</b>	Charlotte Eye Ear Nose & Throat Associates, PA 6035 Fairview Road Charlotte, NC 28210	17
1939	<b>Howard I. Schenker, MD</b>	Rochester Ophthalmological Group, PC 2100 S Clinton Avenue Rochester, NY 14618	23
3807	<b>Steven Marc Silverstein, MD</b>	Silverstein Eye Centers 4240 Blue Ridge BLVD, Suite 1000 Kansas City, MO 64133	3
5471	<b>Inder Paul Singh, MD</b>	Eye Center Of Racine & Kenosha, Ltd. St. Mary' s Medical Center 3805 B Spring Street, Suite 140 Racine, WI 53405	3
3988	<b>Stephen E. Smith, MD</b>	Eye Associates of Fort Myers 4225 Evans Avenue Fort Myers, FL 33901	20
4305	<b>Joseph Sokal, MD</b>	Connecticut Eye Specialists, LLC 4 Corporate Dr., Suite 285 Shelton, CT 06484	7
4311	<b>Navin Tekwani, MD</b>	Tekwani Vision Center Inc. 9911 Kennerly Road, Suite A Saint Louis, MO 63128	18

<b>List of Investigators C-10-039</b>			
<b>Site</b>	<b>Investigator</b>	<b>Address</b>	<b>Subjects Randomized</b>
3626	<b>Michael E. Tepedino, MD</b>	Cornerstone Eye Care 307 N. Lindsay St. High Point, NC 27262	18
2353	<b>George C. Thorne, MD</b>	Eye Physicians of Austin 5011 Burnet Road Austin, TX 78756	25
4424	<b>Robert Treft, MD</b>	Mountain View Eye Center 1580 West Antelope Dr., Suite 175 Layton, Utah 84041	10
1909	<b>Jess Whitson, MD</b>	UT Southwestern Medical Center at Dallas Department of Ophthalmology 5323 Harry Hines Blvd Dallas, TX 75390	5
2600	<b>David Wirta, MD</b>	Eye Research Foundation 520 Superior Avenue Suite, 235 Newport Beach, CA 92663	30

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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MICHAEL J PUGLISI  
10/16/2012

## RPM FILING REVIEW

(Including Memo of Filing Meeting)

**To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]**

Application Information	
NDA # 204251	
Proprietary Name: Simbrinza, tentatively acceptable Established/Proper Name: brinzolamide/brimonidine tartrate Dosage Form: ophthalmic suspension Strengths: brinzolamide 1%, brimonidine tartrate 0.2%	
Applicant: Alcon Pharmaceuticals Agent for Applicant (if applicable):	
Date of Application: June 19, 2012 Date of Receipt: June 19, 2012 Date clock started after UN:	
PDUFA Goal Date: April 19, 2013	Action Goal Date (if different):
Filing Date: August 18, 2012	Date of Filing Meeting: August 7, 2012
Chemical Classification: (1,2,3 etc.) (original NDAs only) 4	
Proposed indication(s)/Proposed change(s): reduction of intraocular pressure in patients with open-angle glaucoma or ocular hypertension	
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)
<b><i>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at: <a href="http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499">http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499</a> and refer to Appendix A for further information.</i></b>	
Review Classification:  <b><i>If the application includes a complete response to pediatric WR, review classification is Priority.</i></b>  <b><i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i></b>	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority  <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>
Part 3 Combination Product? <input type="checkbox"/>  <b><i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i></b>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)

<input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation  <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC  Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (if OTC product):				
List referenced IND Number(s): 106293				
<b>Goal Dates/Product Names/Classification Properties</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
PDUFA and Action Goal dates correct in tracking system?  <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	X			
Are the proprietary, established/proper, and applicant names correct in tracking system?  <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	X			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at: <a href="http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm">http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm</a></i>  <i>If no, ask the document room staff to make the appropriate entries.</i>	X			
<b>Application Integrity Policy</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a></i>		X		
<b>If yes, explain in comment column.</b>				
<b>If affected by AIP, has OC/OMPQ been notified of the submission? If yes, date notified:</b>				
<b>User Fees</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			

<p><u>User Fee Status</u></p> <p><i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i></p>	<p>Payment for this application:</p> <p><input checked="" type="checkbox"/> Paid  <input type="checkbox"/> Exempt (orphan, government)  <input type="checkbox"/> Waived (e.g., small business, public health)  <input type="checkbox"/> Not required</p>																			
<p><i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i></p>	<p>Payment of other user fees:</p> <p><input checked="" type="checkbox"/> Not in arrears  <input type="checkbox"/> In arrears</p>																			
<p><b>505(b)(2)</b>  <b>(NDAs/NDA Efficacy Supplements only)</b></p>	<p><b>YES</b></p>	<p><b>NO</b></p>	<p><b>NA</b></p>	<p><b>Comment</b></p>																
<p>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p>		<p>X</p>																		
<p>Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].</p>		<p>X</p>																		
<p>Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?</p> <p><i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs</i></p>		<p>X</p>																		
<p>Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)?  <i>Check the Electronic Orange Book at:</i>  <a href="http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm">http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</a></p> <p><b>If yes, please list below:</b></p> <table border="1" data-bbox="203 1451 1349 1587"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration														<p>X</p>		
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i></p>																				
<p><b>Exclusivity</b></p>	<p><b>YES</b></p>	<p><b>NO</b></p>	<p><b>NA</b></p>	<p><b>Comment</b></p>																
<p>Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug Designations and Approvals list at:</i>  <a href="http://www.accessdata.fda.gov/scripts/opdlisting/opd/index.cfm">http://www.accessdata.fda.gov/scripts/opdlisting/opd/index.cfm</a></p>		<p>X</p>																		

<p><b>If another product has orphan exclusivity</b>, is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?</p> <p><i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i></p>				
<p>Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>)</p> <p>If yes, # years requested: 3</p> <p><i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i></p>	X			
<p>Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?</p>		X		
<p>If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?</p> <p><i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i></p>				

Format and Content				
<p><i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i></p>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic)  <input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
<p>If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?</p>				
<b>Overall Format/Content</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p>If electronic submission, does it follow the eCTD guidance?<sup>1</sup>            If not, explain (e.g., waiver granted).</p>	X			
<p><b>Index:</b> Does the submission contain an accurate comprehensive index?</p>	X			
<p>Is the submission complete as required under 21 CFR 314.50 (<i>NDAs/NDA efficacy supplements</i>) or under 21 CFR 601.2 (<i>BLAs/BLA efficacy supplements</i>) including:</p>	X			

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<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

<input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)				
<b>If no, explain.</b>				
<b>BLAs only:</b> Companion application received if a shared or divided manufacturing arrangement?				
<b>If yes, BLA #</b>				
<b>Applications in “the Program” (PDUFA V) (NME NDAs/Original BLAs)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Was there an agreement for any minor application components to be submitted within 30 days after the original submission?			<b>X</b>	This application was submitted before the implementation of PDUFA V
<ul style="list-style-type: none"> <li>If yes, were all of them submitted on time?</li> </ul>				
Is a comprehensive and readily located list of all clinical sites included or referenced in the application?				
Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?				
<b>Forms and Certifications</b>				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
<b>Application Form</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	X			
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	X			
<b>Patent Information (NDAs/NDA efficacy supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	X			
<b>Financial Disclosure</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	X			

<p><i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i></p> <p><i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i></p>				
<b>Clinical Trials Database</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p>Is form FDA 3674 included with authorized signature?</p> <p><i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i></p> <p><i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i></p>	X			
<b>Debarment Certification</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p>Is a correctly worded Debarment Certification included with authorized signature?</p> <p><i>Certification is not required for supplements if submitted in the original application; If foreign applicant, <b>both</b> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i></p> <p><i>Note: Debarment Certification should use wording in FD&amp;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..."</i></p>	X			
<b>Field Copy Certification (NDAs/NDA efficacy supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p><b>For paper submissions only:</b> Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>			X	Electronic Submission
<b>Controlled Substance/Product with Abuse Potential</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p><u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff:</i></p> <p><u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i></p>			X	
<b>Pediatrics</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>

<b><u>PREA</u></b>	X			
Does the application trigger PREA?  <i>If yes, notify PeRC RPM (PeRC meeting is required)<sup>2</sup></i>  <i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver &amp; deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i>				
<b>If the application triggers PREA</b> , are the required pediatric assessment studies or a full waiver of pediatric studies included?	X			
<b>If studies or full waiver not included</b> , is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included?  <i>If no, request in 74-day letter</i>			X	
<b>If a request for full waiver/partial waiver/deferral is included</b> , does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)?  <i>If no, request in 74-day letter</i>	X			
<b><u>BPCA</u> (NDAs/NDA efficacy supplements only):</b>  Is this submission a complete response to a pediatric Written Request?  <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)<sup>3</sup></i>		X		
<b>Proprietary Name</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a proposed proprietary name submitted?  <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>	X			
<b>REMS</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a REMS submitted?  <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>			X	
<b>Prescription Labeling</b>	<input type="checkbox"/> <b>Not applicable</b>			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels			

<sup>2</sup> <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

<sup>3</sup> <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

	<input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is Electronic Content of Labeling (COL) submitted in SPL format?  <i>If no, request applicant to submit SPL before the filing date.</i>	X			
Is the PI submitted in PLR format? <sup>4</sup>  <b>If PI not submitted in PLR format</b> , was a waiver or deferral requested before the application was received or in the submission? <b>If requested before application was submitted</b> , what is the status of the request?  <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>	X			
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	X			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send <i>WORD</i> version if available)			X	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	X			
<b>OTC Labeling</b>	<input type="checkbox"/> <b>Not Applicable</b>			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is electronic content of labeling (COL) submitted?  <i>If no, request in 74-day letter.</i>				
Are annotated specifications submitted for all stock keeping units (SKUs)?  <i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined?  <i>If no, request in 74-day letter.</i>				

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
<b>Other Consults</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)		X		
<i>If yes, specify consult(s) and date(s) sent:</i>				
<b>Meeting Minutes/SPAs</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
End-of Phase 2 meeting(s)? <b>Date(s):</b> November 15, 2010 under IND 106293	X			
<i>If yes, distribute minutes before filing meeting</i>				
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? <b>Date(s):</b>		X		
<i>If yes, distribute minutes before filing meeting</i>				
Any Special Protocol Assessments (SPAs)? <b>Date(s):</b>		X		
<i>If yes, distribute letter and/or relevant minutes before filing meeting</i>				

ATTACHMENT

**MEMO OF FILING MEETING**

**DATE:** August 7, 2012

**NDA: 204251**

**PROPRIETARY NAME:** Simbrinza-Tentatively acceptable.

**ESTABLISHED/PROPER NAME:** Brinzolamide/Brimonidine tartrate 1%/0.2%

**DOSAGE FORM/STRENGTH:** ophthalmic suspension

**APPLICANT:** Alcon Research, Ltd.

**PROPOSED INDICATION(S)/PROPOSED CHANGE(S):** reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension

**BACKGROUND:** Clinical studies were conducted under IND 106293. Brinzolamide 1%/brimonidine tartrate 0.2% ophthalmic suspension is a fixed dose combination product of two active components currently approved in the US. This is a 505(b)(2) application, which makes reference to AZOPT, NDA 20816 (brinzolamide 1%, Alcon Research) and ALPHAGAN, NDA 20613 (brimonidine tartrate 0.2%, Allergan). As NDA 20613 is the discontinued from marketing, the applicant provided patent certification for the Bausch & Lomb brimonidine tartrate, 0.2%, ANDA 76260, considered a Reference Listed Drug.

**REVIEW TEAM:** Lucious Lim, Maotang Zhou, Yonghen (Eric) Zhang, Cheryl Dixon, Vinayak Pawar, Tapash Ghosh, Leanna Kelly, Andrew McDougal

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:		
	CPMS/TL:	Judit Milstein	X
Cross-Discipline Team Leader (CDTL)	William Boyd		X
Clinical	Reviewer:	Lucious Lim	X
	Deputy director	Wiley Chambers	X
	Director	Renata Albrecht	X
Social Scientist Review ( <i>for OTC products</i> )	Reviewer:		

	TL:		
OTC Labeling Review ( <i>for OTC products</i> )	Reviewer:		
	TL:		
Clinical Microbiology ( <i>for antimicrobial products</i> )	Reviewer:		
	TL:		

Clinical Pharmacology	Reviewer:	Yongheng Zhang	NO
	TL:	Philip Colangelo	YES
Biostatistics	Reviewer:	Cheryl Dixon	YES
	TL:	Yan Wang	YES
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Andrew McDougal	NO
	TL:	Lori Kotch	YES
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) ( <i>for BLAs/BLA efficacy supplements</i> )	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Maotang Zhou Tapash Ghosh	YES YES
	TL:	Balajee Shanmugam	NO
Quality Microbiology ( <i>for sterile products</i> )	Reviewer:	Vinayak Pawar	NO
	TL:	Brian Riley	NO
CMC Labeling Review	Reviewer:	Leanna Kelly	Yes
	TL:		
Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:	Jung Lee	YES
	PM:	Karen Townsend	YES

OSE/DRISK (REMS)	Reviewer:	Mary Dempsey	YES
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:	Kassa Ayalew	YES
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers			
Other attendees	Daphne Lin, DB4		

**FILING MEETING DISCUSSION:**

<b>GENERAL</b>	
<ul style="list-style-type: none"> <li>505(b)(2) filing issues?</li> </ul> <p><b>If yes, list issues:</b></p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Per reviewers, are all parts in English or English translation?</li> </ul> <p><b>If no, explain:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Electronic Submission comments</li> </ul> <p><b>List comments:</b></p>	<input type="checkbox"/> Not Applicable
<b>CLINICAL</b>	
<p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>Clinical study site(s) inspections(s) needed?</li> </ul> <p><b>If no, explain:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<ul style="list-style-type: none"> <li>Advisory Committee Meeting needed?</li> </ul> <p><b>Comments:</b></p> <p><i>If no, for an NME NDA or original BLA , include the reason. For example:</i></p> <ul style="list-style-type: none"> <li><i>this drug/biologic is not the first in its class</i></li> <li><i>the clinical study design was acceptable</i></li> <li><i>the application did not raise significant safety or efficacy issues</i></li> <li><i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i></li> </ul>	<input type="checkbox"/> YES Date if known: <input type="checkbox"/> NO <input checked="" type="checkbox"/> To be determined  Reason:
<ul style="list-style-type: none"> <li>Abuse Liability/Potential</li> </ul> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>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?</li> </ul> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b>CLINICAL MICROBIOLOGY</b></p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<p><b>CLINICAL PHARMACOLOGY</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>Clinical pharmacology study site(s) inspections(s) needed?</li> </ul>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p><b>BIOSTATISTICS</b></p> <p><b>Comments:</b> There are issues with converting XPT files with file names that include hyphens i.e. -iop-01.xpt to</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter

<p>SAS datasets. The hyphens are not recognized in a manually programmed Proc Copy statement. In an e-mail dated August 9, 2012, the applicant was asked to provide the code necessary to convert XPT files with files names that include hyphens to SAS datasets or any appropriate alternative that will address this issue. The sponsor replied to this request in the submission dated August 10, 2012; Therefore, this request was not included in the 74 day letter</p>	
<p><b>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</b></p> <p><b>Comments:</b></p>	<p><input type="checkbox"/> Not Applicable  <input checked="" type="checkbox"/> FILE  <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><b>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</b></p> <p><b>Comments:</b></p>	<p><input checked="" type="checkbox"/> Not Applicable  <input type="checkbox"/> FILE  <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><b>PRODUCT QUALITY (CMC)</b></p> <p><b>Comments:</b></p>	<p><input type="checkbox"/> Not Applicable  <input checked="" type="checkbox"/> FILE  <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><b><u>Environmental Assessment</u></b></p> <ul style="list-style-type: none"> <li>• Categorical exclusion for environmental assessment (EA) requested?</li> </ul> <p><b>If no</b>, was a complete EA submitted?</p> <p><b>If EA submitted</b>, consulted to EA officer (OPS)?</p> <p><b>Comments:</b></p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES  <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES  <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES  <input type="checkbox"/> NO</p>
<p><b><u>Quality Microbiology (for sterile products)</u></b></p> <ul style="list-style-type: none"> <li>• Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only)</li> </ul>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES  <input type="checkbox"/> NO</p>

<b>Comments:</b>	
<u><b>Facility Inspection</b></u> <ul style="list-style-type: none"> <li>• Establishment(s) ready for inspection?</li> <li>▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ?</li> </ul> <b>Comments:</b>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<u><b>Facility/Microbiology Review (BLAs only)</b></u>  <b>Comments:</b>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<u><b>CMC Labeling Review</b></u>  <b>Comments:</b>	<input type="checkbox"/> Review issues for 74-day letter
<b>REGULATORY PROJECT MANAGEMENT</b>	
<b>Signatory Authority:</b> Renata Albrecht, MD, Division Director  <b>Date of Mid-Cycle Meeting</b> (for NME NDAs/BLAs in “the Program” PDUFA V): TBD  <b>21<sup>st</sup> Century Review Milestones (see attached)</b> (listing review milestones in this document is optional):  <b>Comments:</b>	
<b>REGULATORY CONCLUSIONS/DEFICIENCIES</b>	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing.  <u>Review Issues:</u> <input checked="" type="checkbox"/> No review issues have been identified for the 74-day letter. <input type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional):  <u>Review Classification:</u>

<input checked="" type="checkbox"/>	Standard Review
<input type="checkbox"/>	Priority Review
<b>ACTIONS ITEMS</b>	
<input checked="" type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input type="checkbox"/>	If priority review: <ul style="list-style-type: none"> <li>• notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices)</li> <li>• notify OMPQ (so facility inspections can be scheduled earlier)</li> </ul>
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input checked="" type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	Update the PDUFA V DARRTS page (for NME NDAs in “the Program”)
<input type="checkbox"/>	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST eRoom at: <a href="http://erom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f">http://erom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f</a> ]
<input type="checkbox"/>	Other

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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JUDIT R MILSTEIN  
08/28/2012

# REGULATORY PROJECT MANAGER PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW OF THE PRESCRIBING INFORMATION

To be completed for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Supplements

**Application:** NDA 204-251  
**Application Type:** New NDA  
**Name of Drug:** brinzolamide/brimonidine tartrate ophthalmic suspension 1%/0.2%  
**Applicant:** Alcon Research, Ltd.  
**Submission Date:** June 19, 2012  
**Receipt Date:** June 19, 2012

## 1.0 Regulatory History and Applicant's Main Proposals

The applicant has submitted an original New Drug Application (NDA) for a new fixed-combination ophthalmic suspension of brinzolamide 1% and brimonidine tartrate 0.2%. The proposed indication is the reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension.

## 2.0 Review of the Prescribing Information (PI)

This review is based on the applicant's submitted Microsoft Word format of the PI. The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

## 3.0 Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies see the Appendix.

In addition, the following labeling issues were identified:

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, replace the text in Section 8.4 Pediatric Use with the following statement:

"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)

## **RPM PLR Format Review of the Prescribing Information**

5. Please submit draft carton and container mock-ups for [REDACTED]<sup>(b) (4)</sup> 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 [REDACTED]<sup>(b) (4)</sup> This statement should be removed.

All SRPI format deficiencies of the PI and other labeling issues identified above were conveyed to the applicant in an e-mail dated August 9, 2012. The applicant agreed to submit revised PI in Word format by September 4, 2012. The resubmitted PI will be used for further labeling review.

## 5.0 Appendix

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### Selected Requirements of Prescribing Information (SRPI)

The Selected Requirement of Prescribing Information (SRPI) version 2 is a 48-item, drop-down checklist of critical format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and labeling guidances.

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### Highlights (HL)

#### GENERAL FORMAT

- YES** 1. Highlights (HL) must be in two-column format, with ½ inch margins on all sides and in a minimum of 8-point font.

**Comment:**

- YES** 2. The length of HL must be less than or equal to one-half page (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted in a previous submission (i.e., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is less than or equal to one-half page then select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

➤ **For the Filing Period (for RPMs)**

- *For efficacy supplements:* If a waiver was previously granted, select “YES” in the drop-down menu because this item meets the requirement.
- *For NDAs/BLAs and PLR conversions:* Select “NO” in the drop-down menu because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.

➤ **For the End-of Cycle Period (for SEALD reviewers)**

- The SEALD reviewer documents (based on information received from the RPM) that a waiver has been previously granted or will be granted by the review division in the approval letter.

**Comment:**

- YES** 3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.

**Comment:**

- NO** 4. White space must be present before each major heading in HL.

**Comment:**

- YES** 5. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet).

**Comment:**

## Selected Requirements of Prescribing Information (SRPI)

YES 6. Section headings are presented in the following order in HL:

Section	Required/Optional
• <b>Highlights Heading</b>	Required
• <b>Highlights Limitation Statement</b>	Required
• <b>Product Title</b>	Required
• <b>Initial U.S. Approval</b>	Required
• <b>Boxed Warning</b>	Required if a Boxed Warning is in the FPI
• <b>Recent Major Changes</b>	Required for only certain changes to PI*
• <b>Indications and Usage</b>	Required
• <b>Dosage and Administration</b>	Required
• <b>Dosage Forms and Strengths</b>	Required
• <b>Contraindications</b>	Required (if no contraindications must state "None.")
• <b>Warnings and Precautions</b>	Not required by regulation, but should be present
• <b>Adverse Reactions</b>	Required
• <b>Drug Interactions</b>	Optional
• <b>Use in Specific Populations</b>	Optional
• <b>Patient Counseling Information Statement</b>	Required
• <b>Revision Date</b>	Required

\* RMC only applies to the Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions sections.

*Comment:*

YES 7. A horizontal line must separate HL and Table of Contents (TOC).

*Comment:*

### HIGHLIGHTS DETAILS

#### Highlights Heading

YES 8. At the beginning of HL, the following heading must be **bolded** and appear in all UPPER CASE letters: "**HIGHLIGHTS OF PRESCRIBING INFORMATION**".

*Comment:*

#### Highlights Limitation Statement

YES 9. The **bolded** HL Limitation Statement must be on the line immediately beneath the HL heading and must state: "**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE).**"

*Comment:*

#### Product Title

YES 10. Product title in HL must be **bolded**.

*Comment:*

#### Initial U.S. Approval

YES 11. Initial U.S. Approval in HL must be placed immediately beneath the product title, **bolded**, and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

*Comment:*

## Selected Requirements of Prescribing Information (SRPI)

### Boxed Warning

12. All text must be **bolded**.

Comment:

N/A 13. Must have a centered heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).

Comment:

N/A 14. Must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” centered immediately beneath the heading.

Comment:

N/A 15. Must be limited in length to 20 lines (this does not include the heading and statement “*See full prescribing information for complete boxed warning.*”)

Comment:

N/A 16. Use sentence case for summary (combination of uppercase and lowercase letters typical of that used in a sentence).

Comment:

### Recent Major Changes (RMC)

N/A 17. Pertains to only the following five sections of the FPI: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.

Comment:

N/A 18. Must be listed in the same order in HL as they appear in FPI.

Comment:

N/A 19. Includes heading(s) and, if appropriate, subheading(s) of labeling section(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Dosage and Administration, Coronary Stenting (2.2) --- 3/2012”.

Comment:

N/A 20. Must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

### Indications and Usage

YES 21. If a product belongs to an established pharmacologic class, the following statement is required in the Indications and Usage section of HL: [(Product) is a (name of class) indicated for (indication)].”

Comment:

### Dosage Forms and Strengths

## Selected Requirements of Prescribing Information (SRPI)

- N/A 22. For a product that has several dosage forms, bulleted subheadings (e.g., capsules, tablets, injection, suspension) or tabular presentations of information is used.

Comment:

### Contraindications

- YES 23. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known.

Comment:

- YES 24. Each contraindication is bulleted when there is more than one contraindication.

Comment:

### Adverse Reactions

- YES 25. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

Comment:

### Patient Counseling Information Statement

- YES 26. Must include one of the following three **bolded** verbatim statements (without quotation marks):

If a product **does not** have FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product **has** FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.**”
- “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.**”

*Comment: However, patient labeling was not submitted for this product. Therefore, the phrase, (b) (4) should be deleted from the Patient Counseling Information Statement.*

### Revision Date

- YES 27. **Bolded** revision date (i.e., “**Revised: MM/YYYY or Month Year**”) must be at the end of HL.

Comment:

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## Contents: Table of Contents (TOC)

### GENERAL FORMAT

- NO 28. A horizontal line must separate TOC from the FPI.

Comment:

- YES 29. The following **bolded** heading in all UPPER CASE letters must appear at the beginning of TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”.

Comment:

## Selected Requirements of Prescribing Information (SRPI)

- NO** 30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.  
**Comment:** See the subheadings in the TOC under Section 5 and Section 17.
- N/A** 31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.  
**Comment:**
- YES** 32. All section headings must be **bolded** and in UPPER CASE.  
**Comment:**
- YES** 33. All subsection headings must be indented, not bolded, and in title case.  
**Comment:**
- YES** 34. When a section or subsection is omitted, the numbering does not change.  
**Comment:**
- YES** 35. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “**FULL PRESCRIBING INFORMATION: CONTENTS**” must be followed by an asterisk and the following statement must appear at the end of TOC: “\*Sections or subsections omitted from the Full Prescribing Information are not listed.”  
**Comment:**

## Full Prescribing Information (FPI)

### GENERAL FORMAT

- YES** 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: “**FULL PRESCRIBING INFORMATION**”.  
**Comment:**
- YES** 37. All section and subsection headings and numbers must be **bolded**.  
**Comment:**
- YES** 38. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

<b>Boxed Warning</b>
<b>1 INDICATIONS AND USAGE</b>
<b>2 DOSAGE AND ADMINISTRATION</b>
<b>3 DOSAGE FORMS AND STRENGTHS</b>
<b>4 CONTRAINDICATIONS</b>
<b>5 WARNINGS AND PRECAUTIONS</b>
<b>6 ADVERSE REACTIONS</b>
<b>7 DRUG INTERACTIONS</b>
<b>8 USE IN SPECIFIC POPULATIONS</b>
<b>8.1 Pregnancy</b>
<b>8.2 Labor and Delivery</b>
<b>8.3 Nursing Mothers</b>
<b>8.4 Pediatric Use</b>
<b>8.5 Geriatric Use</b>

## Selected Requirements of Prescribing Information (SRPI)

<b>9 DRUG ABUSE AND DEPENDENCE</b>
<b>9.1 Controlled Substance</b>
<b>9.2 Abuse</b>
<b>9.3 Dependence</b>
<b>10 OVERDOSAGE</b>
<b>11 DESCRIPTION</b>
<b>12 CLINICAL PHARMACOLOGY</b>
<b>12.1 Mechanism of Action</b>
<b>12.2 Pharmacodynamics</b>
<b>12.3 Pharmacokinetics</b>
<b>12.4 Microbiology (by guidance)</b>
<b>12.5 Pharmacogenomics (by guidance)</b>
<b>13 NONCLINICAL TOXICOLOGY</b>
<b>13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility</b>
<b>13.2 Animal Toxicology and/or Pharmacology</b>
<b>14 CLINICAL STUDIES</b>
<b>15 REFERENCES</b>
<b>16 HOW SUPPLIED/STORAGE AND HANDLING</b>
<b>17 PATIENT COUNSELING INFORMATION</b>

**Comment:**

- N/A 39. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under Section 17 (Patient Counseling Information). All patient labeling must appear at the end of the PI upon approval.

**Comment:**

- N/A 40. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, [*see Warnings and Precautions (5.2)*].

**Comment:**

- N/A 41. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

**Comment:**

### FULL PRESCRIBING INFORMATION DETAILS

#### Boxed Warning

- N/A 42. All text is **bolded**.

**Comment:**

- N/A 43. Must have a heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).

**Comment:**

- N/A 44. Use sentence case (combination of uppercase and lowercase letters typical of that used in a sentence) for the information in the Boxed Warning.

**Comment:**

#### Contraindications

- N/A 45. If no Contraindications are known, this section must state “None”.

## Selected Requirements of Prescribing Information (SRPI)

### Comment:

#### Adverse Reactions

- YES** 46. When clinical trials adverse reactions data is included (typically in the “Clinical Trials Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

*“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.”*

### Comment:

- N/A** 47. When postmarketing adverse reaction data is included (typically in the “Postmarketing Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

*“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”*

### Comment:

#### Patient Counseling Information

- N/A** 48. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:
- “See FDA-approved patient labeling (Medication Guide)”
  - “See FDA-approved patient labeling (Medication Guide and Instructions for Use)”
  - “See FDA-approved patient labeling (Patient Information)”
  - “See FDA-approved patient labeling (Instructions for Use)”
  - “See FDA-approved patient labeling (Patient Information and Instructions for Use)”

### Comment:

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/s/  
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LEANNA M KELLY  
08/21/2012

JUDIT R MILSTEIN  
08/21/2012  
NDA 204251-Initial Labeling review