CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
22-134

OTHER REVIEW(S)

M E M O R A N D U M

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

CLINICAL INSPECTION SUMMARY

DATE: June 07, 2010

TO: William Boyd, MD, Cross Discipline Team Leader
Division of Anti-Infective and Ophthalmology Products

FROM: Kassa Ayalew, M.D.
Good Clinical Practice Branch II
Division of Scientific Investigations
Phone: (301) 796-0670
FAX: (301) 847-8748
Email: kassa.ayalew@fda.hhs.gov

THROUGH: Tejashri Purohit-Sheth, M.D.
Branch Chief, Good Clinical Practice Branch II
Division of Scientific Investigations

SUBJECT: Clinical Inspection Summary

NDA#: 22-134

DRUG: alcaftadine ophthalmic solution 0.25%, (b) (4)

NME: Yes

REVIEW PRIORITY: Standard

INDICATIONS: Prevention of itching associated with allergic conjunctivitis

CONSULTATION REQUEST DATE: 10/29/2009

PDUFA: 7/28/2010

ACTION GOAL DATE: 6/28/2010

I. BACKGROUND:

The sponsor, Vistakon Pharmaceuticals, L.L.C., submitted a new drug application (NDA) for (b) (4) (alcaftadine ophthalmic solution) 0.25%. The purpose of this application submitted on September 29, 2009 was to support the labeling claim for the prevention of itching associated with allergic conjunctivitis.

The product (b) (4) (Alcaftadine) is a H1, H2, and H4 histamine receptor antagonist intended for the prevention of itching associated with allergic conjunctivitis. Because of its longer duration of action (>12 hours), it is intended for once daily administration for the treatment of ocular allergic reactions.

The Applicant has provided data from 4 pivotal clinical trials (Protocol No.: 09-003-05, Protocol No.: 05-003-11, Protocol No.: 05-003-10 and Protocol No.: 05-003-13), which they believe provide sufficient evidence for the safety and efficacy of (b) (4) (alcaftadine ophthalmic solution) 0.25%. The two protocols inspected to assess data integrity and human subject protection were Protocol No.: 09-003-05 and Protocol No.: 05-003-11.

Protocol No.: 05-003-11: was a Multi-Center, Double-Masked, Randomized, Placebo Controlled, Evaluation of the Onset and Duration of Action of R89674 0.25% Ophthalmic Solution in the Conjunctival Allergen Challenge (CAC) Model of Acute Allergic Conjunctivitis. The study was a double-masked, randomized, Vehicle-controlled study to evaluate the onset and duration of action of (b) (4) 0.25% ophthalmic solution in the CAC model of acute allergic conjunctivitis. The objective of this study was to establish the efficacy of (b) (4) 0.25% ophthalmic solution compared to Vehicle in preventing the signs and symptoms of conjunctival allergen challenge-induced allergic conjunctivitis at 16 hours (Visit 3) following medication instillation and at 15 minutes (Visit 4) following medication instillation.

A total of 126 subjects were reportedly enrolled across 5 centers in the United States and 123 subjects completed the study. Randomized subjects were to be assigned to receive either Vehicle (placebo) ophthalmic solution administered bilaterally (Vehicle/Vehicle; N=44), (b) (4) 0.25% ophthalmic solution administered bilaterally ((b) (4) N=40), or (b) (4) 0.25% ophthalmic solution in one eye and Vehicle (placebo) in the fellow eye (Vehicle/ (b) (4) N=42).

Protocol No.: 09-003-05: was a Prospective, Multi-Center, Double-Masked, Randomized, Vehicle-Controlled Evaluation of the Onset and Duration of Action of R89674 0.25% Ophthalmic Solution Compared to Vehicle in the Conjunctival Allergen Challenge (CAC) Model of Acute Allergic Conjunctivitis

The study was a double-masked, randomized, Vehicle-controlled study to evaluate the onset and duration of action of (b) (4) 0.25% ophthalmic solution in the CAC model of acute allergic conjunctivitis. The objective of this study was to establish the efficacy of (b) (4) 0.25% ophthalmic solution compared to Vehicle in preventing the signs and symptoms of CAC-induced allergic conjunctivitis at 16 hours (Visit 3) following medication instillation and at 15 minutes (Visit 4) following medication instillation.

Eligible subjects were to be randomly assigned to one of the following treatment arms:

- (b) (4) 0.25% ophthalmic solution administered bilaterally
- Vehicle (placebo) ophthalmic solution administered bilaterally

A total of 109 subjects were reportedly screened and 60 subjects were eligible for randomization across the two centers that enrolled subjects (Edward Meier, MD; Mason, OH and Thomas Macejko, MD; Fairfield, OH), both located in the United State; 58 subjects were reported to have completed the study.

Four domestic clinical investigators were selected for inspection of the two pivotal studies described above, to assess data integrity and human subject protection. The four sites were selected due to high enrollment.

II. RESULTS (by Site):

Name of CI, IRB, or Sponsor Location	Protocol #/Site/ # of Subjects	Inspection Date	Final Classification
Mundorf, Thomas K., M.D. Mundorf Eye Center 1718 E. Fourth St., Suite 703 Charlotte, NC 28204 Phone: (704) 334-3222 tommundorf@aol.com	Protocol 05-003-11 Mundorf Eye Center/ 36	December 17 - 21, 2009	NAI
Edward Meier, MD Eye Care Associates of Greater Cincinnati, Inc. 5378D Cox Smith Road Mason, OH 45040	Protocol 09-003-05 Center 1/ 30	January 19- 22, 2010	NAI
Vistakon Division Of Johnson & Johnson Vision Care, Inc. 7500 Centurion Parkway, Suite 100 Jacksonville, FL 32256	Protocol 09-003-05/ Vistakon/30 Protocol 05-003-11/Vistakon/ 36	March 15 – March 18, 2010	VAI
(b) (4)		December 22 and 23, 2009	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. Mundorf, Thomas K., M.D.
Mundorf Eye Center
1718 E. Fourth St., Suite 703
Charlotte, NC 28204

a. **What was inspected**:
This inspection was performed as a data audit for NDA 22-134. This inspection was conducted in accordance with Compliance Program 7348.811 between December 17 and 21, 2009.

At this site 50 subjects were screened and 37 were enrolled. Thirty-six (36) subjects completed the study. No deaths or adverse events were reported. The inspection covered 100% review of informed consent documents for 36/37 enrolled subjects. Thirty-five (35) subject records were audited. The site audit included, but was not limited to, CRFs, primary efficacy values, concomitant medications and drug dispensing records, adverse events, IRB/Ethics committee correspondence, sponsor correspondence, monitoring reports, and test article accountability. No significant issues concerning the clinical investigator site were identified during the inspection, and a Form FDA 483 was not issued.

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

b. **General observations/commentary**:

The inspection of Dr. Mundorf's site revealed that the study was conducted in accordance with the investigational plan. A Form FDA 483, Inspectional Observations, was not issued.

c. **Assessment of data integrity**:
There were no regulatory violations noted by the FDA inspector. In general, based on review of the provided Establishment Inspection Report (EIR) for this site, data derived from Dr. Mundorf's site are considered a reliable.

2) Edward Meier, MD
Eye Care Associates of Greater
Cincinnati, Inc.
5378D Cox Smith Road
Mason, OH 45040

a. What was inspected:

At this site 50 subjects were screened and 30 were enrolled. Twenty-nine (29) subjects completed the study. One subject (#01021 (b) (4)) withdrew consent due to a non-related SAE event, thyroid removal surgery. No deaths or adverse events were reported.

The inspection covered 100% review of all informed consent documents for all subjects screened and enrolled. Thirty (30) subject records were audited in depth. Documents reviewed in the audit included, medical records, regulatory documents, case report forms, adverse events, and source documents. There were no limitations to the inspection.

b. General observations/commentary:
The inspection of Dr. Meier's site did not reveal regulatory violations. No significant issues concerning the clinical investigator site were identified during the inspection, and a Form FDA 483 was not issued.

c. Assessment of data integrity:
Based on review of the provided Establishment Inspection Report (EIR) and the documents submitted with that report, we conclude that data derived from Dr. Meier's site are considered acceptable.

3) (b) (4)

a. What was inspected:

This CRO inspection was conducted in accordance with Compliance Program 7348.811 between December 22 and 23, 2009. Vistakon Pharmaceuticals, LLC had transferred the following responsibilities to (b) (4): selection of qualified investigators; conducting study initiation and protocol training; selection of monitors; monitoring, conduct and supervision of ongoing investigators; biostatistics and data analysis; collection and review of safety information and transfer of data to Vistakon; informing FDA, clinical investigators, and Vistakon of all serious adverse events or risks with respect to the study drug; and preparation of final clinical reports. The purpose of the inspection, which was conducted in accordance with the Sponsor/Monitor/Contract Research Organization (CRO) compliance program, was to review sponsor/CRO activities conducted in support of this application.

The inspection audited and focused on clinical investigators, Thomas Mundorf, M.D. (Charlotte, NC), and Edward Meier, M.D., (Manson, OH).

A total of 12 case report forms from the 115 subjects that completed the two studies listed in the background section were randomly chosen and were reviewed for clinical investigators Thomas Mundorf, M.D. (Charlotte, NC), and Edward Meier, M.D., (Manson, OH).

Review of records included, but was not limited to sponsor organization and associated contracted firms, data handling and entry, clinical investigator selection and training procedures, monitor selection processes, monitoring procedures and activities, site-specific data (including enrollment numbers, adverse events, concomitant medications, and study medications), quality assurance activities, adverse event reporting, and study drug reconciliation. There were no limitations to the inspection.

b. General observations/commentary:
No objectionable conditions were observed during the inspection. No refusals were encountered. No significant observations of noncompliance were noted. The CRO appears to have executed their contractually obligated responsibilities adequately. No Form FDA 483 was issued.

d. Assessment of data integrity:
Based on review on the provided Establishment Inspection Report (EIR) from this CRO inspection, the data are considered acceptable.

4) Vistakon Division Of Johnson & Johnson Vision Care, Inc
7500 Centurion Parkway,
Suite 100
Jacksonville, FL 32256

a. What was inspected:

This Sponsor inspection was conducted in accordance with Compliance Program 7348.811 between March 15 and 18, 2010. The purpose of the inspection was to review sponsor activities conducted in support of this application. The inspection audited and focused on clinical investigators Thomas Mundorf, M.D. (Charlotte, NC), and Edward Meier, M.D., (Manson, OH).

During the inspection, the sponsor provided copies of the two sites' screening/enrollment logs : the log from the study conducted by Dr. Mundorf (Study 05-003-11; 50 subjects screened & 36 subjects enrolled) and the log from the study conducted by Dr Meier (Study 09-003-05;50 subjects screened & 30 subjects enrolled).

Review of records included data listings provided with this assignment for the two study sites found that the number of enrolled subjects and subject identification numbers matched the site enrollment logs. There were no limitations to the inspection.

b. General observations/commentary:

The inspection of Vistakon Division Of Johnson & Johnson Vision Care, Inc or the Sponsor's inspection site revealed that the study was not conducted in accordance with the investigational plan. A Form FDA 483, Inspectional Observations, was issued to this Sponsor for in recordkeeping and record retention issues. The following regulatory violations were observed during the inspection:

- Failure in recordkeeping and record retention [21 CFR 312.60].

  The sponsor's drug reconciliation documentation did not indicate that all bottles of the study drug packed, shipped, and used in the study were accounted for in the return and destruction of the product. In addition there was no documentation on the disposition of study drugs not shipped to the

clinical investigator sites and retained at the facility performing the labeling, shipping and destruction of the study drug. The sponsor's inventory of unlabeled study drug from the 2009 study (Protocol #09-003-05) found that the firm was missing one bottle of the study drug. The sponsor should have maintained adequate records showing the receipt, shipment, or other disposition of the investigational drug.

e. Assessment of data integrity:

Although regulatory violations were noted by the FDA inspector, it is unlikely that these findings would affect subject safety or data integrity. In general, based on the provided Establishment Inspection Report (EIR) for this site, data received from Vistakon Division Of Johnson & Johnson Vision Care, Inc are considered a reliable.

IV. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Two clinical sites, the sponsor, and a CRO were inspected in support of this application. Based on inspection of the studies and source documents at Dr. Mundorf, Dr. Meier, (b) (4) and Division of Johnson & Johnson Vision Care, Inc., the efficacy and safety data obtained from these sites appear to be reliable, and can be used in support of application.

{See appended electronic signature page}

Kassa Ayalew, M.D.
Good Clinical Practice Branch II
Division of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Tejashri Purohit-Sheth, M.D.
Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22134	ORIG-1	VISTAKON PHARMACEUTICALS LLC	(b) (4) OPHTHALMIC SOLUTION

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

/s/

KASSA AYALEW
06/09/2010
Tejashri: please sign. Thanks, Kassa

TEJASHRI S PUROHIT-SHETH
06/09/2010

SEALD LABELING REVIEW

APPLICATION NUMBER	NDA 22-134
APPLICANT	Vistakon Pharmaceuticals, LLC
DRUG NAME	(b) (4) (alcaftadine ophthalmic solution)
SUBMISSION DATE	September 29, 2009
SEALD REVIEW DATE	May 11, 2010
SEALD REVIEWER(S)	Debbie Beitzell, BSN
	This review does not identify all guidance-related labeling issues and all best practices for labeling. We recommend the review division become familiar with those recommendations. This review does attempt to identify all aspects of the draft labeling that do not meet the requirements of 21 CFR 201.56 and 201.57.

8 pp of draft labeling withheld in full immediately after this page as (b)(4) CCI/TS.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22134	ORIG-1	VISTAKON PHARMACEUTICALS LLC	(b) (4) OPHTHALMIC SOLUTION

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

/s/

DEBRA C BEITZELL
05/11/2010
SEALD comments sent to DAIOP on 5/11/10.

LAURIE B BURKE
05/11/2010

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	February 17, 2010
To:	Wiley Chambers, MD, Acting Director Division of Anti-infective and Ophthalmology Products
Through:	Melina Griffis, RPh, Team Leader Denise Toyer, PharmD, Deputy Director Carol Holquist, RPh, Director Division of Medication Error Prevention and Analysis
From:	Anne Crandall, PharmD, Safety Evaluator Division of Medication Error Prevention and Analysis
Subject:	Label and Labeling Review
Drug Name(s):	(b) (4) (Alcaftadine) Ophthalmic Solution, 0.25%
Application Type/Number:	NDA 022134
Applicant/sponsor:	Vistakon Pharmaceuticals
OSE RCM #:	2009-1813

CONTENTS

INTRODUCTION

The Division of Medication Error Prevention and Analysis evaluated the proposed container label, carton and insert labeling for (b) (4) (NDA 022134) and identified vulnerabilities that could lead to medication errors. We provide recommendations in Section 2 with the aim of reducing the risk of medication errors with regards to the proposed product label and labeling.

1 METHODS AND MATERIALS REVIEWED

Using Failure Mode and Effects Analysis (FMEA),[1] the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the container labels, carton labeling and insert labeling submitted as part of the October 28, 2009 original NDA submission. See Appendix A and B for images of proposed container labels and carton labeling.

2 CONCLUSION AND RECOMMENDATIONS

Our evaluation of the proposed container labels and carton labeling noted areas of needed improvement in order to minimize the potential for medication errors. We request the recommendations for the container labels and carton labeling in Section 2.1 be communicated to the Applicant prior to approval.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications on this review, please contact the OSE Regulatory Project Manager, Brantley Dorch, at 301-796-0150.

2.1 COMMENTS TO THE APPLICANT

A. (b) (4) 0.25% Container Label and Carton Labeling (1 mL and 3 mL)

The colors chosen for the container label and carton labeling, green and yellow, correspond with specific drug classes of ophthalmic medications (miotics and beta-blockers, respectively) of which this product does not belong. As a result, the yellow and green may cause confusion among providers and patients regarding the mechanism of action of this product. Therefore choosing colors that are unassigned to drug classes may cause less confusion among providers and patients.

3 pp of draft labeling withheld in full immediately after this page as (b)(4) CCI/TS.

[1] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

AS APPEARS ON ORIGINAL

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22134	ORIG-1	VISTAKON PHARMACEUTICALS LLC	(b) (4) OPHTHALMIC SOLUTION

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

/s/

ANNE CRANDALL
02/17/2010

MELINA N GRIFFIS
02/17/2010

DENISE P TOYER
02/18/2010

DENISE P TOYER on behalf of CAROL A HOLQUIST
02/18/2010

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements (except SE8 and SE9)

Application Information		
NDA # 22-134	NDA Supplement #:S-	Efficacy Supplement Type SE-
Proprietary Name: (b) (4) Established/Proper Name: alcaftadine ophthalmic solution Dosage Form: solution Strengths: 0.25%		
Applicant: Vitakon Pharmaceuticals, LLC Agent for Applicant (if applicable): Lorna-Jane Bremer		
Date of Application: September 29, 2009 Date of Receipt: September 29, 2009 Date clock started after UN: N/A		
PDUFA Goal Date: July 28, 2010	Action Goal Date (if different): May 30, 2010	
Filing Date: November 28, 2009	Date of Filing Meeting: October 30, 2009	
Chemical Classification: (1,2,3 etc.) (original NDAs only) 1 (NME)		
Proposed indication(s)/Proposed change(s): for the prevention of itching associated w/ allergic conjunctivitis.		

Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***If 505(b)(2): Draft the "505(b)(2) Assessment" form found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/ucm027499.html*** ***and refer to Appendix A for further information.***	☒ 505(b)(1) ☐ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)
Review Classification: ***If the application includes a complete response to pediatric WR, review classification is Priority.*** ***If a tropical disease priority review voucher was submitted, review classification is Priority.***	☒ Standard ☐ Priority ☐ Tropical Disease Priority Review Voucher submitted
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐
Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☐ Drug/Biologic ☐ Drug/Device ☐ Biologic/Device
☐ Fast Track ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical

Other:	benefit and safety (21 CFR 314.610/21 CFR 601.42)
Collaborative Review Division (*if OTC product*):	
List referenced IND Number(s): 66,884	

Goal Dates/Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA and Action Goal dates correct in tracking system? ***If not, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	**X**			
Are the proprietary, established/proper, and applicant names correct in tracking system? ***If not, 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.***	**X**			
Are all classification properties [e.g., orphan drug, 505(b)(2)] entered into tracking system? ***If not, ask the document room staff to make the appropriate entries.***	**X**			
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***		**X**		
If yes, explain in comment column.			**X**	
If affected by AIP, has OC/DMPQ been notified of the submission? **If yes,** date notified:			**X**	
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	**X**			

User Fee Status ***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 UN letter and contact user fee staff.***	Payment for this application: ☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
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.	Payment of other user fees: ☒ Not in arrears ☐ In arrears

Note: *505(b)(2) applications are no longer exempt from user fees pursuant to the passage of FDAAA. All 505(b) applications, whether 505(b)(1) or 505(b)(2), require user fees unless otherwise waived or exempted (e.g., small business waiver, orphan exemption).*

505(b)(2) **(NDAs/NDA Efficacy Supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?		**X**		
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (see 21 CFR 314.54(b)(1)).				
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))? ***Note:*** *If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9).*		**X**		
Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.fda.gov/cder/ob/default.htm*** **If yes**, please list below:		**X**		

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

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 108(b)(2).Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.

Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product have orphan exclusivity for the same indication? ***Check the Electronic Orange Book at:*** ***http://www.fda.gov/cder/ob/default.htm***		**X**		
If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007)***			**X**	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ***(NDAs/NDA efficacy supplements only)*** **If yes**, # years requested: 3 years ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	**X**			

Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (***NDAs only***)?		**X**		
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)? ***If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.***				

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☐ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
If electronic submission, does it follow the eCTD guidance[1]? **If not,** explain (e.g., waiver granted).	**X**			
Index: Does the submission contain an accurate comprehensive index?	**X**			
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including: ☒ legible ☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only) **If no**, explain.	**X**			
Controlled substance/Product with abuse potential: Is an Abuse Liability Assessment, including a proposal for scheduling, submitted? ***If yes,*** *date consult sent to the Controlled Substance Staff:*		**X**		
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #			**X**	

Forms and Certifications				
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.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature? ***If foreign applicant, <u>both</u> the applicant and the U.S. agent must sign the form.***	**X**			
Are all establishments and their registration numbers listed on the form/attached to the form?	**X**			
Patent Information **(NDAs/NDA efficacy supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a?	**X**			
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature? ***Forms must be signed by the APPLICANT, not an Agent.*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*	**X**			
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature?	**X**			
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature? ***(Certification is not required for supplements if submitted in the original application)*** ***If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification.*** ***Note:*** *Debarment Certification should use wording in FD&C Act section 306(k)(l) 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…"*	**X**			

Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***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)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***	**X**			

Pediatrics	YES	NO	NA	Comment
PREA Does the application trigger PREA? ***If yes, notify PeRC RPM (PeRC meeting is required)*** ***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 & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.*	**X**			
If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?	**X**			
If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? ***If no, request in 74-day letter***		**X**		
If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required under 21 CFR 314.55(b)(1), (c)(2), (c)(3)/21 CFR 601.27(b)(1), (c)(2), (c)(3) ***If no, request in 74-day letter***	**X**			
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)***		**X**		

Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that it is submitted as a separate document and routed directly to OSE/DMEPA for review.***	**X**			
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☐ Medication Guide (MedGuide) ☐ Carton labels ☐ Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request in 74-day letter.***	**X**			
Is the PI submitted in PLR format?	**X**			
If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request PLR format in 74-day letter.***				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC?	**X**			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*)		**X**		
REMS consulted to OSE/DRISK?				
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA?	**X**			
OTC Labeling	☒ **Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***	**X**			

Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***		**X**		
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***		**X**		
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?	**X**			
Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:***	**X**			DSI Consult

Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** ***If yes, distribute minutes before filing meeting***				
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** ***If yes, distribute minutes before filing meeting***				
Any Special Protocol Assessments (SPAs)? **Date(s):** ***If yes, distribute letter and/or relevant minutes before filing meeting***				

[1] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

ATTACHMENT

MEMO OF FILING MEETING

DATE: 10/30/2009

BLA/NDA/Supp #: 22-134

PROPRIETARY NAME: (b) (4)

ESTABLISHED/PROPER NAME: alcaftadine ophthalmic solution

DOSAGE FORM/STRENGTH: 0.25%

APPLICANT: Vistakon Pharmaceuticals, LLC

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): for the prevention of itching associated w/ allergic conjunctivitis

BACKGROUND:

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	RodriguezR	Y
	CPMS/TL:	DillonParkerM	N
Cross-Discipline Team Leader (CDTL)	BoydW		N
Clinical	Reviewer:	NevittM	Y
	TL:	ChambersW	Y
Social Scientist Review (*for OTC products*)	Reviewer:	N/A	
	TL:	N/A	
OTC Labeling Review (*for OTC products*)	Reviewer:	N/A	
	TL:	N/A	
Clinical Microbiology (*for antimicrobial products*)	Reviewer:	N/A	
	TL:	N/A	

Clinical Pharmacology	Reviewer:	ZhangY	Y
	TL:	BonapaceC	Y
Biostatistics	Reviewer:	ZhuangD	Y
	TL:	WangY	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:		
	TL:	SchmidtW	Y
Statistics (carcinogenicity)	Reviewer:	N/A	
	TL:	N/A	
Immunogenicity (assay/assay validation) *(for BLAs/BLA efficacy supplements)*	Reviewer:	N/A	
	TL:	N/A	
Product Quality (CMC)	Reviewer:	ZhouM	Y
	TL:	NgL	Y
Quality Microbiology *(for sterile products)*	Reviewer:	PawarV	N
	TL:	McVeyJ	N
CMC Labeling Review *(for BLAs/BLA supplements)*	Reviewer:	N/A	
	TL:	N/A	
Facility Review/Inspection	Reviewer:		
	TL:	CharityA	Y
OSE/DMEPA (proprietary name)	Reviewer:	DorchB	Y
	TL:		
OSE/DRISK (REMS)	Reviewer:	N/A	
	TL:	N/A	
Bioresearch Monitoring (DSI)	Reviewer:	AyalewK	Y
	TL:		

Other reviewers		
Other attendees		

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues? **If yes,** list issues:	☒ Not Applicable ☐ YES ☐ NO
• Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO
• Electronic Submission comments **List comments**:	☐ Not Applicable
CLINICAL **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain:	☒ YES ☐ NO
• Advisory Committee Meeting needed? **Comments**: NME ***If no, for an original NME or BLA application, include the reason. For example:*** o ***this drug/biologic is not the first in its class*** o ***the clinical study design was acceptable*** o ***the application did not raise significant safety or efficacy issues*** o ***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***	☐ YES Date if known: ☐ NO ☒ To be determined Reason:

• 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? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
CLINICAL MICROBIOLOGY **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☒ NO
BIOSTATISTICS **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
IMMUNOGENICITY (BLAs/BLA efficacy supplements only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC)	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter

Comments:	

Environmental Assessment • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)? **Comments**:	☐ Not Applicable ☒ YES ☐ NO ☐ YES ☐ NO ☐ YES ☐ NO
Quality Microbiology (for sterile products) • Was the Microbiology Team consulted for validation of sterilization? (**NDAs/NDA supplements only**) **Comments**:	☐ Not Applicable ☒ YES ☐ NO
Facility Inspection • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? **Comments**:	☐ Not Applicable ☒ YES ☐ NO ☒ YES ☐ NO
Facility/Microbiology Review (BLAs only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CMC Labeling Review (BLAs/BLA supplements only) **Comments**:	☐ Review issues for 74-day letter

REGULATORY PROJECT MANAGEMENT	
Signatory Authority: **21st Century Review Milestones (see attached)** (optional): **Comments**:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. Review Issues: ☒ No review issues have been identified for the 74-day letter. ☐ Review issues have been identified for the 74-day letter. List (optional): Review Classification: ☒ Standard Review ☐ Priority Review
ACTIONS ITEMS	
☐	Ensure that the review and chemical classification properties, as well as any other pertinent properties (e.g., orphan, OTC) are correctly entered into tracking system.
☐	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
☐	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.
☐	BLA/BLA supplements: If filed, send 60-day filing letter
☐	If priority review: • 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) • notify DMPQ (so facility inspections can be scheduled earlier)
☒	Send review issues/no review issues by day 74
☐	Other

Appendix A (NDA and NDA Supplements only)

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

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

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

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

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

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

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),

(2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.

(3) All other “criteria” are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

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

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

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

(3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22134	ORIG-1	VISTAKON PHARMACEUTICALS LLC	(b) (4) OPHTHALMIC SOLUTION

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

/s/

RAPHAEL R RODRIGUEZ
11/20/2009

DSI CONSULT: Request for Clinical Inspections

Date: October 29, 2009

To: Tejashri Purohit-Sheth, M.D.
Kassa Ayalew, M.D.
Division of Scientific Investigations, HFD-45
Office of Compliance/CDER

Through: William Boyd, M.D., Clinical Team Leader & Medical Officer
Division of Anti-Infective and Ophthalmology Products

From: Raphael Rodriguez, Regulatory Health Project Manager
Division of Anti-Infective and Ophthalmology Products

Subject: **Request for Clinical Site Inspections**

General Information

Application#: **NDA 22-134**
Sponsor/Sponsor contact information (to include phone/email):
Vistakon Pharmaceuticals, L.L.C.
Stephen Holcroft, 904-443-1613

Drug: **(alcaftadine ophthalmic solution) 0.25%**
Trade Name: (b) (4)
NME: **Yes**
Standard or Priority: Standard
Proposed indication: prevention of itching associated with allergic conjunctivitis
PDUFA: **7/28/2010**
Action Goal Date: **6/28/2010**
Inspection Summary Goal Date: **5/28/2010**

Protocol/Site Identification

Include the Protocol Title/# for all protocols to be audited. Complete the following table.

Site # (Name,Address, Phone number, email, fax#)	Protocol #	Number of Subjects	Indication
DSI choice	Study 05-003-11 Study 09-003-05	126 60	prevention of itching associated with allergic conjunctivitis

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

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.
__X__ Other (specify): Routine Inspections

Goal Date for Completion:
We request that the inspections be performed and the Inspection Summary Results be provided by 5/29/2010**.** We intend to issue an action letter on this application by 6/29/2010. The PDUFA due date for this application is 7/29/2010**.**

Should you require any additional information, please contact Raphael Rodriguez at 301-796-0798 or William Boyd, MD at 301-796-0686.

Additional Information:

This is an electronic NDA. 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.

Note that the highest enroller in Study 05-003-11 is Thomas Mundorf, MD, who enrolled 36 subjects.

Note each investigator in Study 09-003-05: Edward Meier, MD, and Thomas Macejko, MD enrolled 30 subjects.

05-003-11			
	Inv. #	**Principal Investigator and Address**	**# Randomized**
1	06	Thomas Mundorf, MD Mundorf Eye Center 1718 E. Fourth St., Suite 703 Charlotte, NC 28204	36
2	08	Francis Price, MD Price Vision Group 9002 North Meridian Indianapolis, IN 46260	31
3	07	John Lonsdale, MD Central Maine Eye Care, P.A. 181 Russel St. Lewiston, ME 04240	23
4	*	Stacey Ackerman, MD Philadelphia Eye Associates 1703 S. Broad St. Philadelphia, PA 19148	20
5	*	Howard Schenker, MD Rochester Ophthalmologic Group, PC 2100 South Clintion Ave. Rochester, NY 14618	16

* Investigator site numbers requested from applicant.

09-003-05			
	Inv. #	**Principal Investigator and Address**	**# Randomized**
1	01	Edward Meier, MD Eye Care Associates of Greater Cincinnati, Inc. 5378D Cox Smith Road Mason, OH 45040	30
2	02	Thomas Macejko, MD Eye Care Associates of Greater Cincinnati, Inc. 563 Wessel Drive Fairfield, OH 45014	30

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22134	ORIG-1	VISTAKON PHARMACEUTICALS LLC	(b) (4) OPHTHALMIC SOLUTION

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

/s/

RAPHAEL R RODRIGUEZ
10/29/2009