

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-134

CHEMISTRY REVIEW(S)

MEMORANDUM

Date: June 24, 2010

To: NDA 22-134

From: Stephen P. Miller, Ph.D.
Acting Chief, Branch V
Pre-marketing Assessment Division II
ONDQA

Subject: ONDQA Branch Chief Recommendation for NDA 22-134 (b) (4) (alcaftadine Ophthalmic Solution, 0.25%)

The CMC review of NDA 22-134 was finalized by Maotang Zhou on June 21, 2010 with a recommendation for “approval, pending satisfactory review from the Product Quality Microbiology perspective.”

The Product Quality Microbiology review was finalized on June 22, 2010 with a recommendation for approval.

There are no Post-Marketing Commitments in either of these two reviews.

NDA 22-134 is recommended for approval based on all aspects of drug substance and drug product quality.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22134	ORIG-1	VISTAKON PHARMACEUTICA LS LLC	ALCAFTADINE OPHTHALMIC SOLUTION 0.25%

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/s/

STEPHEN P MILLER
06/24/2010

MEMORANDUM

Date: June 24, 2010

To: NDA 22-134

From: Terrance Ocheltree, Ph.D., R. Ph.
Division Director
Division II, ONDQA

Subject: Tertiary review of ONDQA recommendation for NDA 22-134 (b) (4)
(alcaftadine ophthalmic solution) 0.25%

I have assessed the ONDQA review of NDA 22-134 by Maotang Zhou. The review was finalized on June 21, 2010 with a recommendation for “approval, pending satisfactory review from the Product Quality Microbiology perspective.” The Product Quality Microbiology review was finalized on June 22, 2010 with a recommendation for approval. All proposed manufacturing and testing sites have “Acceptable” site recommendation as shown in EES. Therefore, NDA 22-134 is recommended for approval based on all aspects of drug substance and drug product quality.

No post marketing commitments are proposed in either of the ONDQA or the Product Quality Microbiology reviews.

NDA 22-134 is for an ophthalmic solution containing 2.5 mg/mL (0.25%) alcaftadine in an isotonic solution. The proposed commercial packaging includes a 5 mL dropper bottle with a 3 mL fill for the trade product and a 1 mL fill for professional samples. The expiry period for the commercial product (3 mL fill in a 5 mL bottle) is 24 months when stored at 15-25°C (59-77°F), while the expiry period for the professional sample (1 mL fill in a 5 mL bottle) is 14 months when stored at 15-25°C (59-77°F) (b) (4)

I concur with the approval recommendation from a CMC perspective without any post marketing commitments.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22134	ORIG-1	VISTAKON PHARMACEUTICA LS LLC	ALCAFTADINE OPHTHALMIC SOLUTION 0.25%

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/s/

TERRANCE W OCHELTREE
06/24/2010

NDA 22-134

(b) (4)

(alcaftadine ophthalmic solution) 0.25%

Vistakon Pharmaceuticals, LLC

Maotang Zhou, Ph.D.

Division of Pre-Marketing Assessment II

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Chemistry Review Data Sheet

1. NDA 22-134
2. REVIEW #2
3. REVIEW DATE: 21-June-2010
4. REVIEWER: Maotang Zhou, Ph.D.
5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Original Submission	29-Sep-2009

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original Submission	29-Sep-2009
Telephone Amendment	10-Dec-2009
Telephone Amendment	29-Jan-2010
Telephone Amendment	31-Mar-2010
Telephone Amendment	22-Apr-2010
Telephone Amendment	29-Apr-2010
Telephone Amendment	03-May-2010
Telephone Amendment	07-May-2010
Telephone Amendment	26-May-2010

7. NAME & ADDRESS OF SPONSOR:

Vistakon Pharmaceuticals, LLC
 7500 Centurion Parkway, Suite 100
 Jacksonville, FL 32256
 Tel. 904-443-1631
 Fax: 904-928-5578

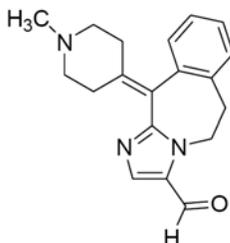
Lorna-Jane Bremer
 Johnson & Johnson Consumer & Personal
 Products Worldwide
 185 Tabor Road
 Morris Plains, NJ 07950
 Tel: 973-385-0557
 Fax: 973-385-4300

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: (b) (4)
- b) Non-Proprietary Name (USAN): Alcaftadine

Chemistry Review Data Sheet

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)
10. PHARMACOLOGICAL CATEGORY: Ophthalmic
11. DOSAGE FORM: Ophthalmic solution
12. STRENGTH/POTENCY: 0.25%
13. ROUTE OF ADMINISTRATION: Topical Ophthalmic Solution
14. Rx/OTC DISPENSED: Rx
15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\)](#): N/A
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:
 6,11-dihydro-11-(1-methyl-4-piperidinylidene)-5H-imidazo[2,1-b] [3] benzazepine-3-Carboxaldehyde
 $C_{19}H_{21}N_3O$
 MW: 307.39



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	REVIEW DATE	COMMENT
20066	II	Cilag AG	Alcaftadine	1	Adequate	5/11/2010 (M.Zhou)	
(b) (4)	III	(b) (4)	(b) (4)	4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			

¹ Action codes for DMF Table:

Chemistry Review Data Sheet

- 1 – DMF Reviewed.
- 2 –Type 1 DMF
- 3 – Reviewed previously and no revision since last review
- 4 – Sufficient information in application
- 5 – Authority to reference not granted
- 6 – DMF not available
- 7 – Other (explain under "Comments")
- 2 Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

IND-66884

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	Pending	---	Vinayak Pawar
EES	Acceptable	04/23/2010	E Johnson
Methods Validation	N/A	---	---
Labeling	Acceptable	06/07/2010	NDA Review Team
Bioequivalence	N/A	---	---
EA	Categorical Exclusion	---	---
Radiopharmaceutical	N/A	---	---

19. ORDER OF REVIEW

This NDA was granted standard review.

The Chemistry Review for ANDA

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA has provided sufficient/adequate information to assure identity, strength, purity, and quality of the drug product from the CMC perspective; however, a review from the Product Quality Microbiology perspective is still pending.

An "Acceptable" site recommendation from the Office of Compliance has been made.

The labels have adequate information as required.

Therefore, from the CMC perspective, this NDA is recommended for approval, pending satisfactory review from the Product Quality Microbiology perspective.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Substance

The drug substance, Alcaftadine, is a white to yellow powder, with a molecular formula of $C_{19}H_{21}N_3O$ and a molecular weight of 307.39 Daltons. The drug substance is a new molecular entity developed in the Janssen Research Foundation, and has not been previously marketed. Alcaftadine is the assigned INN name. Alcaftadine drug substance is manufactured, controlled, packaged, and stability-tested at Cilag AG, Switzerland. The information of manufacturing processes and controls for alcaftadine drug substance is described in Cilag's DMF 20066. Johnson & Johnson Pharmaceutical Research and Development, L.L.C. is the US agent for Cilag AG. Stability testing was performed by Cilag AG and release testing performed by (b) (4). A letter of authorization to refer to DMF 20066 was provided on behalf of Cilag AG. DMF 20066 has been reviewed and all chemistry issues have been resolved. The DMF is adequate as modified to support the current NDA.

Drug Product

The drug product, alcaftadine 2.5 mg/mL ophthalmic solution, is an isotonic solution for a once daily dosing regimen in the prevention of itching associated with allergic

Executive Summary Section

conjunctivitis. The ophthalmic solution is formulated with a (b) (4) buffer to obtain a pH of 7.0, benzalkonium chloride is added as a preservative, and edetate disodium dihydrate (EDTA) is used as a chelating agent (b) (4). All the excipients are of compendial grade.

The drug product solution is manufactured by (b) (4). This site is also responsible for release and stability testing of the drug product. The company responsible for development, registration and commercialization is Vistakon Pharmaceuticals, LLC.

The proposed commercial packaging includes a 5 mL (with 3 mL fill for trade and 1 mL fill for professional samples) low-density polyethylene (LDPE) white bottle with a corresponding (b) (4) white dropper tip, a white polypropylene cap, and a shrink tamper evident band with pressure adhesive label. The white cap is in accordance with the recommended AAO color scheme. Container closure system is sterilized by (b) (4).

At the time of the NDA submission, 12-month long term and 6-month accelerated stability data were provided; and the stability testing is expected to continue to 30 months. The 18-month stability data were provided during the review cycle at the request by the FDA. In reviewing the primary registration stability data, it can be seen that in the first few months there is a considerable decreasing trend in pH and assay, and an increasing trend in identified individual impurities and total impurities. The sponsor attributed the initial fast degradation of the drug substance to the interaction of alcaftadine with the (b) (4) LDPE bottles. Based on the results from the statistical analysis of the 18-month stability data, the sponsor initially proposed a 24-month expiry period for (b) (4) 3 mL fill size products, however, after much discussion with the FDA, the sponsor has agreed to (b) (4) the expiry period for the physician's sample (1 mL fill in a 5 mL bottle) (b) (4) to 14 months (b) (4). The sponsor has also agreed to implement a 14 month stability time point at 25°C/40%RH for its commercial stability commitment. The expiry period for the commercial product (3 mL fill in a 5 mL bottle) will remain to be 24 months. Both products will be stored at 15-25°C (59-77°F).

The mock up labels and package inserts are submitted. As amended, the labels and package inserts have adequate information as required by 21 CFR 201.10.

B. Description of How the Drug Product is Intended to be Used

(b) (4) ® is a clear, sterile ophthalmic solution containing alcaftadine 2.5 mg/mL (0.25%) intended for topical administration to the eye. The sponsor seeks approval of alcaftadine ophthalmic solution, 0.25% for a once daily dosing regimen in the prevention of itching associated with allergic conjunctivitis. The sponsor believes that alcaftadine ophthalmic solution, 0.25%, with its once-a-day dosing regimen is expected to offer the

Executive Summary Section

patient advantages in terms of convenience which could lead to enhanced treatment compliance.

C. Basis for Approvability or Not-Approval Recommendation

The sponsor has provided sufficient information on raw material controls, manufacturing processes and process controls, and adequate specifications for assuring consistent product quality of the drug substance and drug product. The sponsor has also provided sufficient stability information on the drug product to assure strength, purity, and quality of the drug product during the expiration dating period. A review from the Product Quality Microbiology perspective is still pending.

All facilities have “Acceptable” site recommendations.

All labels have the required information.

III. Administrative**A. Reviewer’s Signature**

Maotang Zhou, Ph.D, Chemistry Reviewer

B. Endorsement Block

Stephen Miller, Ph.D. Acting Branch Chief

C. CC Block

48 pp withheld in full immediately following this page as (b)(4) CCI/TS.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22134	ORIG-1	VISTAKON PHARMACEUTICA LS LLC	ALCAFTADINE OPHTHALMIC SOLUTION 0.25%

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/s/

MAOTANG ZHOU

06/21/2010

A review from Product Quality Microbiology's perspective is pending.

STEPHEN P MILLER

06/21/2010

A CMC Branch Chief memo will be issued for this NDA once the Product Quality Microbiology review is completed.

NDA 22-134

(b) (4)

(alcaftadine ophthalmic solution) 0.25%

Vistakon Pharmaceuticals, LLC

Maotang Zhou, Ph.D.

Division of Pre-Marketing Assessment II

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Chemistry Review Data Sheet

1. NDA 22-134
2. REVIEW #1
3. REVIEW DATE: 12-May-2010
4. REVIEWER: Maotang Zhou, Ph.D.
5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Original Submission	29-Sep-2009

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original Submission	29-Sep-2009
Telephone Amendment	10-Dec-2009
Telephone Amendment	29-Jan-2010
Telephone Amendment	31-Mar-2010
Telephone Amendment	22-Apr-2010
Telephone Amendment	29-Apr-2010
Telephone Amendment	03-May-2010
Telephone Amendment	07-May-2010

7. NAME & ADDRESS OF APPLICANT:

Vistakon Pharmaceuticals, LLC
 7500 Centurion Parkway, Suite 100
 Jacksonville, FL 32256
 Tel. 904-443-1631
 Fax: 904-928-5578

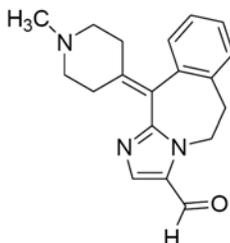
Lorna-Jane Bremer
 Johnson & Johnson Consumer & Personal
 Products Worldwide
 185 Tabor Road
 Morris Plains, NJ 07950
 Tel: 973-385-0557
 Fax: 973-385-4300

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: (b) (4)
- b) Non-Proprietary Name (USAN): Alcaftadine

Chemistry Review Data Sheet

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)
10. PHARMACOLOGICAL CATEGORY: Ophthalmic
11. DOSAGE FORM: Ophthalmic solution
12. STRENGTH/POTENCY: 0.25%
13. ROUTE OF ADMINISTRATION: Topical Ophthalmic Solution
14. Rx/OTC DISPENSED: Rx
15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\)](#): N/A
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:
 6,11-dihydro-11-(1-methyl-4-piperidinylidene)-5H-imidazo[2,1-b] [3] benzazepine-3-Carboxaldehyde
 $C_{19}H_{21}N_3O$
 MW: 307.39



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	REVIEW DATE	COMMENT
20066	II	Cilag AG	Alcaftadine	1	Adequate	5/11/2010 (M.Zhou)	
(b) (4)	III		(b) (4)	4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			

¹ Action codes for DMF Table:

Chemistry Review Data Sheet

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- 2 –Type 1 DMF
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- 6 – DMF not available
- 7 – Other (explain under "Comments")
- 2 Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

IND-66884

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A	---	---
EES	Acceptable	04/23/2010	E Johnson
Methods Validation	N/A	---	---
Labeling	Not Acceptable		
Bioequivalence	N/A	---	---
EA	Categorical Exclusion	---	---
Radiopharmaceutical	N/A	---	---

19. ORDER OF REVIEW

This NDA was granted standard review.

The Chemistry Review for ANDA

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA has not provided sufficient/adequate information to assure identity, strength, purity, and quality of the drug product. The applicant needs to respond to the CMC recommendations made in the IR letter dated May 10, 2010. These issues include expiration dating period for the physician sample (first communicated in the IR letter dated April 21, 2010).

The Product Quality Microbiology review needs to be finalized with a recommendation about the acceptability of the controls on microbial limits and the sterilization process.

An "Acceptable" site recommendation from the Office of Compliance has been made.

The labeling issues are still pending as of the date of this review.

Therefore, from the CMC perspective, this NDA is not recommended for approval until all pending issues are resolved.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Substance

The drug substance, Alcaftadine, is a white to yellow powder, with a molecular formula of $C_{19}H_{21}N_3O$ and a molecular weight of 307.39 Daltons. The drug substance is a new molecular entity developed in the Janssen Research Foundation, and has not been previously marketed. Alcaftadine is the assigned INN name. Alcaftadine drug substance is manufactured, controlled, packaged, and stability-tested at Cilag AG, Switzerland. The information of manufacturing processes and controls for alcaftadine drug substance is described in Cilag's DMF 20066. Johnson & Johnson Pharmaceutical Research and Development, L.L.C. is the US agent for Cilag AG. Stability testing was performed by Cilag AG and release testing performed by (b) (4) A letter of authorization to refer to DMF 20066 was provided on behalf of Cilag AG. DMF

Executive Summary Section

20066 has been reviewed and all chemistry issues have been resolved. The DMF is adequate as modified to support the current NDA.

Drug Product

The drug product, alcaftadine 2.5 mg/mL ophthalmic solution, is an isotonic solution for a once daily dosing regimen in the prevention of itching associated with allergic conjunctivitis. The ophthalmic solution is formulated with a (b) (4) buffer to obtain a pH of 7.0, benzalkonium chloride is added as a preservative, and edetate disodium dihydrate (EDTA) is used as a chelating agent (b) (4).

All the excipients are of compendial grade.

The drug product solution is manufactured by (b) (4). This site is also responsible for release and stability testing of the drug product. The company responsible for development, registration and commercialization is Vistakon Pharmaceuticals, LLC.

The proposed commercial packaging includes a 5 mL (with 3 mL fill for trade and 1 mL fill for professional samples) low-density polyethylene (LDPE) white bottle with a corresponding (b) (4) white dropper tip, a white polypropylene cap, and a shrink tamper evident band with pressure adhesive label. The white cap is in accordance with the recommended AAO color scheme. Container closure system is sterilized by (b) (4).

At the time of the NDA submission, 12-month long term and 6-month accelerated stability data were provided; and the stability testing is expected to continue to 30 months. The 18-month stability data were provided during the review cycle at the request by the FDA. In reviewing the primary registration stability data, it can be seen that in the first few months there is a considerable decreasing trend in pH and assay, and an increasing trend in identified individual impurities and total impurities. The applicant attributed the initial fast degradation of the drug substance to the interaction of alcaftadine with the (b) (4) LDPE bottles. Based on the results from the statistical analysis of the 18-month stability data, the applicant proposed a 24-month expiry period for (b) (4) 3 mL fill size products; however, FDA recommends a (b) (4) (4)-month expiry period for the 1 mL fill product (b) (4). This issue has not been resolved as of the date of this review.

The mock up labels were submitted; however, the proprietary name, (b) (4) has not been accepted by FDA. The applicant is expected to submit an alternate proprietary name for consideration. In addition, two CMC recommended modifications on the PI have not been made by applicant as of the date of this review.

B. Description of How the Drug Product is Intended to be Used

Executive Summary Section

(b) (4)® is a clear, sterile ophthalmic solution containing alcaftadine 2.5 mg/mL (0.25%) intended for topical administration to the eye. The applicant seeks approval of alcaftadine ophthalmic solution, 0.25% for a once daily dosing regimen in the prevention of itching associated with allergic conjunctivitis. The applicant believes that alcaftadine ophthalmic solution, 0.25%, with its once-a-day dosing regimen is expected to offer the patient advantages in terms of convenience which could lead to enhanced treatment compliance.

C. Basis for Approvability or Not-Approval Recommendation

This NDA has provided sufficient information on raw material controls, manufacturing processes and process controls, and adequate specifications for assuring consistent product quality of the drug substance and drug product. However, the NDA has not provided sufficient stability information on the drug product to assure strength, purity, and quality of the drug product during the expiration dating period.

All facilities have “Acceptable” site recommendations.

The labeling issues are still pending as of the date of this review.

III. Administrative**A. Reviewer’s Signature**

Maotang Zhou, Ph.D, Chemistry Reviewer

B. Endorsement Block

Stephen Miller, Ph.D. Acting Branch Chief

C. CC Block

46 pp 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
PHARMACEUTICA
LS 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/

MAOTANG ZHOU
05/14/2010

STEPHEN P MILLER
05/14/2010
I concur

Initial Quality Assessment
Branch IV
Pre-Marketing Assessment Division II

OND Division: Division of Anti-Infective and Ophthalmology Products
NDA: 22-134
Applicant: Vistakon Pharmaceutical LLC
Stamp Date: September 29, 2009
PDUFA Date: July 29, 2010
Trademark: (b) (4)™
Established Name: Alcaftadine ophthalmic solution 0.25%
Dosage Form: Ophthalmic Solution 0.25% as base
Route of Administration: topical
Indication: Prevention of itching and allergic conjunctivitis

PAL: Linda Ng, Ph.D.

	YES	NO
ONDQA Fileability:	<input checked="" type="checkbox"/>	<input type="checkbox"/>
Comments for 74-Day Letter	<input type="checkbox"/>	<input checked="" type="checkbox"/>

Summary and Critical Issues:

Summary

The official NDA was submitted September 29, 2009 and was accepted as a 1S submission. The amendment dated October 6, 2009 contains a pediatric partial waiver and does not contain any CMC information. The drug substance is a new molecular entity developed in the Janssen Research Foundation, and has not been previously marketed. Alcaftadine is the assigned INN name. The requested indication is the prevention of itching and allergic conjunctivitis.

Alcaftadine is manufactured by Cilag AG, Switzerland. Though this is not manufactured by the NDA holder, information related to the drug substance was submitted in the NDA with detailed information in the DMF 20,066. Johnson & Johnson Pharmaceutical Research and Development, L.L.C. is the US agent for Cilag AG. Stability testing was performed by Cilag AG and release testing performed by (b) (4). Alcaftadine is claimed to be a white to yellow powder with slight solubility in water. No polymorphic form was stated to be found but no details of study seem to be provided. Reference standard, post-approval commitment and stability data were included in the DMF, but not in the NDA.

The drug product, 2.5 mg/mL at pH 7, is formulated as a preserved isotonic solution (b) (4) by (b) (4). This site is also responsible for release and stability testing of the drug product. Benzalkonium chloride and edetate disodium dihydrate are in the formulation. All excipients are compendial. Batch size is (b) (4).

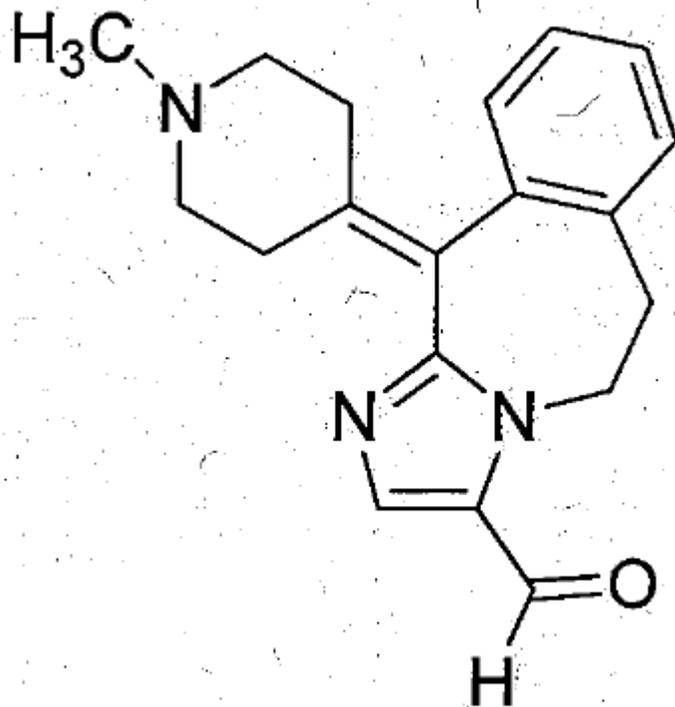
No overage was used. The product is 3 mL fill for trade and 1 mL fill for physician in a 5 mL white LDPE bottle with natural tip, and white polypropylene cap, shrink tamper evident band with pressure adhesive label. The white cap is in accordance with the recommended AAO color scheme. Container closure system is sterilized by (b) (4)

Three batches of each fill size, stored horizontally, of stability testing for 12 months were submitted; and testing is expected to continue to 30 months. Regression analysis was performed and predicted to support the (b) (4) months expiry requested. Thermal cycling study, photostability study, forced degradation study, and in-use study were evaluated.

Mock-up labels are provided.

Dr. Vinayak Pawar is the assigned microbiology reviewer. Mr. Raphael Rodriguez, OND PM, submitted the trade name request to DMEP and the labeling consult to DDMAC on October 26, 2009. Jeannie David, ONDQA PM, working with Dr. Maotang Zhou has submitted the EER on October 30, 2009.

The structure and properties of the drug substance are listed:



Molecular Formula

C₁₉H₂₁N₃O

Molecular Weight

307.39 Daltons

Critical issues for review

- The applicant's proposal for starting material was rejected in EOP2 meeting. No agreement was reached. Reviewer should follow up on the decision on starting material.
- Polymorphism is stated to be not an issue, but no data could be found to support that statement. This may not be important for current solution formulation, but will be if the dosage form contains the drug substance in the solid state for future NDAs.
- Acceptance criteria and tests in the drug substance specification should be evaluated for safety, meaningfulness, and manufacturing capability, e.g., microbial limits, it is unclear what "objectionable organisms" are.
- Characterization of the reference standard should be confirmed for quality.
- Reviewer should review validity of the relative response factor (RRF) for the impurities in the drug substance.
- The drug product formulation contains compendial excipients that include purified water. Purified water has been acceptable for sterile ophthalmic products until challenged by a citizen's petition. Many NDAs have since come in with Water for Injection instead of Purified water. Reviewer should check status.
- Qualification of container closure system only performed using USP <87>, <88> and <661>. The applicant should include a one-time study for freeze-thaw cycling study, extraction study through expiry and a water loss study through expiry. With future cc change, the studies may need to be repeated. These studies appear to be missing. The latter two studies were recommended in the EOP2 meeting.
- Stability studies did not include upright position but only horizontal position. The storage conditions used are 25°C/40% RH, 30°C/65% RH, and 40°C/NMT 25% RH. The intermediate humidity condition for the 30°C should be 35%RH instead of 65% RH. If the formulated solution is stable, a trend in assay and impurities should be observed with the water loss. Reviewer should evaluate.
- The drug product stability protocol does not contain an adequate commitment. It should state to inform the division and to reference the CFR for FDA contact in case of failure. That is, the applicant should also inform the OND Division when "a distributed batch does not meet the approved NDA specifications at the real time storage condition (25°C/40%RH)".
- The acceptance criteria of drug product tests should be reviewed for meaningful conditions and criteria. The Any Individual Unspecified Impurity for the drug product is expected to be NMT (b) (4) in the ophthalmic drug product. Test and criterion for endotoxin are missing.
- It is suggested that a system suitability test to include a standard at the quantitation limit to ensure detectability of impurities at that level. This system suitability test should be included for both drug substance and drug product impurities test. Reviewer should evaluate that the impurity tests should include useful system suitability testing in each analytical procedure.
- The Relative Response Factor for the impurities testing of the drug product should be evaluated for reliability.
- The package insert contains NDC numbers for both the physician sample and trade size. Reviewer should check if this is acceptable. In general, information on the physician sample is not included in the PI.

- Comments for 74-Day Letter

None recommended.

D. Review, Comments and Recommendation:

The NDA is acceptable for filing. Since this is a standard review, no team review is recommended. Dr. Maotang Zhou has been assigned to review the NDA.

____ Linda Ng, Ph.D. _____
Pharmaceutical Assessment Lead

Date

____ Stephen Miller, Ph.D. _____
Acting Branch Chief

Date

cc: OND PM RRodriguez
ONDQA PM JDavid

=====
Appendix 1: Formulations

Table 3.2.P.1-1 Composition of Drug Product, Formula PD-F-5525

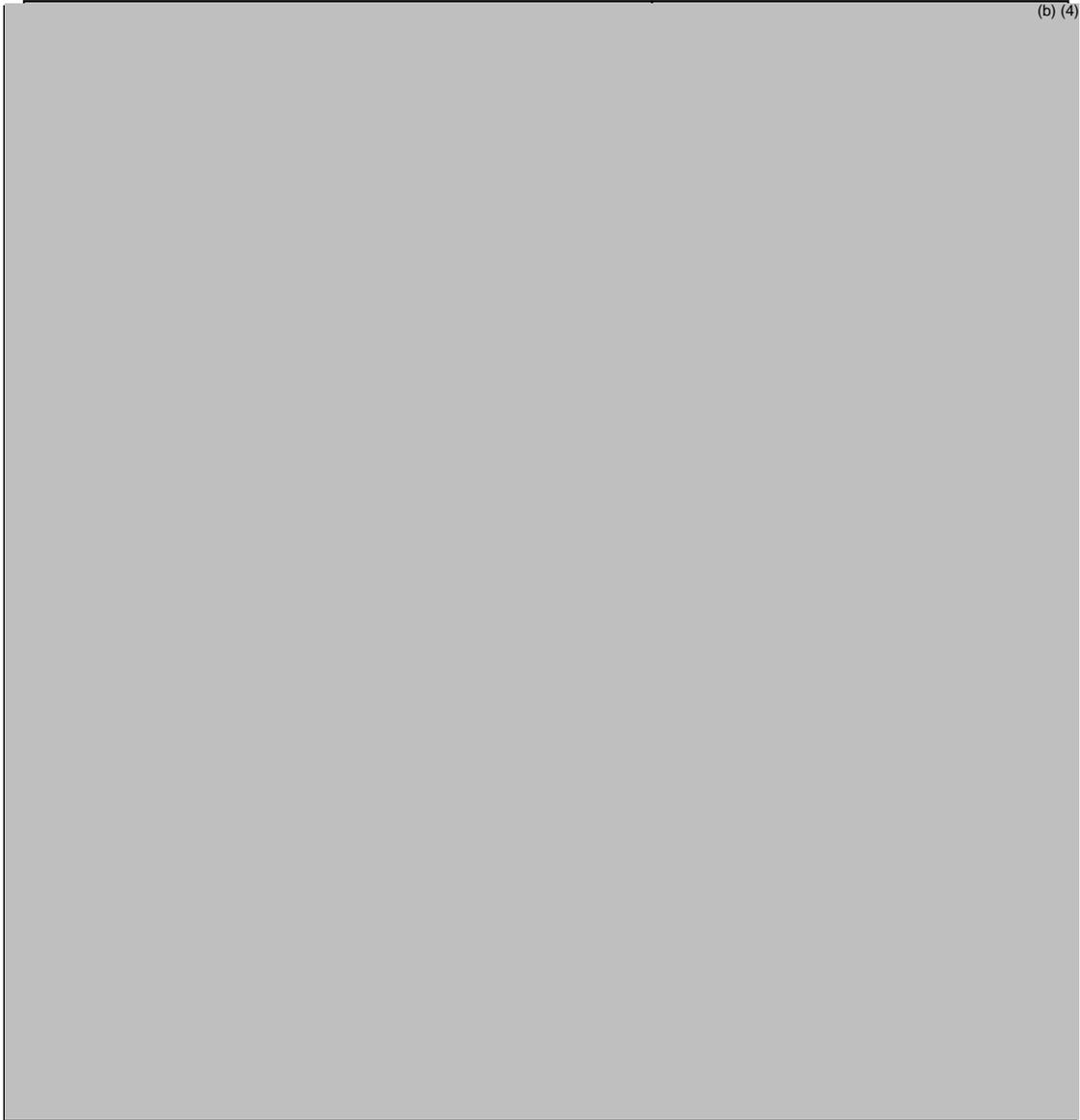
Components	Reference to Quality Standard	Function	Concentration mg/mL
Alcaftadine	In-House	Active Ingredient	2.5
Sodium Phosphate Monobasic Monohydrate	USP		(b) (4)
Edetate Disodium, Dihydrate	USP		
Benzalkonium Chloride (50% Solution) ¹	NF	Preservative	(b) (4)
Sodium Chloride	USP		(b) (4)
Sodium Hydroxide (1N Solution) ²	NF	pH Adjustment	pH Adjustment Target 7.0
Hydrochloric Acid (1N Solution) ²			
Purified Water	USP		(b) (4)

¹ Equivalent to 0.05 mg/mL Benzalkonium Chloride.

² If needed, 1N NaOH solution and/or 1N HCl solution may be added to adjust the pH to 7.0.

Appendix 2: Drug Substance Specification
Table 3.2.S.4.1-1 Alcaftadine Specifications

(b) (4)



* Release specification only.

Appendix 3: Drug Product Specification

Table 3.2.P.5.1-1 Drug Product Specifications

(b) (4)

* Release Test Only

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22134

ORIG-1

VISTAKON
PHARMACEUTICA
LS LLC

(b) (4) OPHTHALMIC
SOLUTION

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/s/

LINDA L NG
11/11/2009

STEPHEN P MILLER
11/23/2009

NDA FILEABILITY CHECKLIST

NDA Number: 22-134

Applicant: Vistakon Pharmaceutical LLC

Letter Date: September 29, 2009

Stamp Date: September 29, 2009

Drug Name: (b) (4)™ (alcaftadine ophthalmic solution) 0.25%

IS THE CMC SECTION OF THE APPLICATION FILEABLE? (Yes or No) Yes

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies.

	Parameter	Yes	No	Comment
1	On its face, is the section organized adequately?	Y		
2	Is the section indexed and paginated adequately?	Y		This is an eCTD NDA
3	On its face, is the section legible?	Y		
4	Are ALL of the facilities (including contract facilities and test laboratories) identified with full <u>street</u> addresses and CFNs?	Y		Seems to be. Contains FEI/CFN, phone and fax # and occasionally contact name. Firm will be asked to confirm list by ONDQA PM
5	Is a statement provided that all facilities are ready for GMP inspection?			Not able to locate
6	Has an environmental assessment report or categorical exclusion been provided?	Y		Claims categorical exclusion 1.12.14
7	Does the section contain controls for the drug substance?	Y		Alcaftadine supplied by Cilag AG., Switzerland DMF 20066. Stability data & commitment submitted in the DMF.
8	Does the section contain controls for the drug product?	Y		Section 3.2.P.5.
9	Has stability data and analysis been provided to support the requested expiration date?	Y		One strength with 2 fill sizes of 1 mL, and 3 mL in 5 mL bottle. Total of 3 batches for each fill for 12 months stability RT, 30°C and accelerated. No info on position - horizontal or/and upright. No expiry claim for 1 mL physician. Trade planned for (b) (4) or 24 months expiry. Supportive longer stability data.
10	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	Y		Not much asked. Section 1.12.4
11	Have draft container labels been provided?	Y		Section 1.14.1
12	Has the draft package insert been provided?	Y		Section 1.14.1
13	Has an investigational formulations section been provided?	Y		Section 3.2.P.2
14	Is there a Methods Validation package?		N	No separate package. Information included in section 3.2.P.5.3.
15	Is a separate microbiological section included?		N	No separate section; information incorporated in CMC section

NDA 22-134

Chemistry Reviewer:
Pharmaceutical Assessment Lead:
Acting Branch Chief:
Prepared by: LN 10/13/09

Maotang Zhou, Ph.D.
Linda Ng, Ph.D.
Stephen Miller, Ph.D.

DMF Number	Holder	Description	LOA Included	Status
20066	Cilag AG.	Alcaftadine	August 25, 2009	
			(b) (4) June 9, 2009	
			August 6, 2009	
			June 3, 2009	
			June 3, 2009	
			February 12, 2009	
			September 3, 2009	
			June 4, 2009	
			June 5, 2009	

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/s/

LINDA L NG
10/21/2009

STEPHEN P MILLER
10/26/2009
Concur