CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
22-134

OFFICE DIRECTOR MEMO

Deputy Office Director Decisional Memo

Date	(electronic stamp)
From	John Farley, M.D.,M.P.H.
Subject	Deputy Office Director Decisional Memo
NDA #	22-134
Applicant Name	Vistakon Pharmaceuticals, LLC
Date of Submission	September 29, 2009
PDUFA Goal Date	July 29, 2010
Proprietary Name / Established (USAN) Name	Lastacaft / alcaftadine ophthalmic solution, 0.25%
Dosage Forms / Strength	Topical ophthalmic solution
Proposed Indication	Indicated for the prevention of itching associated with allergic conjunctivitis
Action:	Approval

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Martin P. Nevitt, M.D., M.P.H.
Statistical Review	Dongliang Zhuang Ph.D., Yan Wang, Ph.D.
Pharmacology Toxicology Review	James S. Wild, Ph.D., Wendelyn Schumdt, Ph.D.
CMC Review	Maotang Zhou, Ph.D., Stephen P. Miller, Ph.D., Terrence Ocheltree Ph.D., R.Ph.
Product Quality Microbiology Review	Vinayak B. Pawar, Ph.D. Stephen Langille, Ph.D.
Clinical Pharmacology Review	Yongheng Zhang, Ph.D., Charles Bonapace, Pharm.D.
DDMAC	Nisha Patel, Pharm.D., Sheila Ryan, Pharm. D.
DSI	Kassa Ayalew, M.D.
CDTL Review	William M. Boyd, M.D.
OSE/DMEPA	Anne Crandall, Pharm. D.
SEALD	Debbie Beitzell, BSN
Division Director Review	Wiley A. Chamber, M.D.

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
DSI=Division of Scientific Investigations
CDTL=Cross-Discipline Team Leader
OSE= Office of Surveillance and Epidemiology
DEPi= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management

1. Introduction

The drug substance alcaftadine is a H_1 histamine antagonist and inhibitor of the release of histamine from mast cells. The molecular formula is $C_{19}H_{21}N_3O$. This new molecular entity was developed originally by the Janssen Research Foundation. The drug product is a sterile ophthalmic solution containing 2.5 mg/mL alcaftadine.

The proposed indication is the prevention of itching associated with allergic conjunctivitis.

The proposed dosing regimen is to instill one drop in each eye once daily.

The proposed proprietary name is Lastacaft.

The efficacy review for this NDA relies upon the results of three adequate and well-controlled conjunctival antigen challenge (CAC) studies, 05-003-11, 05-003-13, and 09-003-05.

The review team has reviewed issues pertinent to their respective disciplines with regard to the safety and efficacy of alcaftadine ophthalmic solution 0.25% for the indication proposed. For a detailed discussion of NDA 22-134, the reader is referred to individual discipline specific reviews, the Cross-Discipline Team Leader Review, and the Division Director Review.

2. Background/Regulatory

Studies 05-003-11 and 05-003-13 were CAC studies completed in subjects > 10 years of age using the original formulation of the drug product. These studies failed for prevention of ocular redness, but were successful for prevention of itching. Following completion of these studies, the drug product formulation was modified to include a reduction in the buffer concentration, preservative and chelating agent (in order to improve overall comfort of the product). With the change in formulation, the Division requested an additional efficacy trial to support this change. Study 06-003-09 was a 6 week environmental study with the modified formulation. Study 06-003-09 failed, likely related to many of the subjects enrolled exhibiting no itching or redness during the course of the study. Subsequently, study 09-003-05, a CAC study with the new formulation, was carried out. In addition, the applicant carried out study 05-003-10, a 6 week safety study using the original formulation.

There is no previous marketing experience with alcaftadine ophthalmic solution 0.25% as the proposed active ingredient has not been previously approved in the U.S. or abroad.

This is the initial NDA application for this product.

3. Chemistry Manufacturing and Controls / Product Quality Microbiology

All CMC reviewers concluded that the NDA provided sufficient information to assure identity, strength, purity, and quality of the drug product and recommended approval. The application was recommended for approval from the product quality microbiology standpoint. There are no outstanding CMC issues.

An "Acceptable" site recommendation from the Office of Compliance based on site inspections was made.

The DMF was reviewed by Dr. Zhou and determined to be adequate as modified to support the NDA.

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 EDTA is used as a chelating agent (b) (4) All the excipients are of compendial grade. The proposed commercial packaging includes a 5 mL bottle (with 3 mL fill for trade and 1 mL fill for professional samples). Due to stability concerns with the 1 mL fill, a 14 month stability time point has been agreed to for the 1 mL fill professional sample and an expiry of 24 months has been agreed to for the 3 mL fill.

The manufacturing process consists of (b) (4) The formulation met standards for inhibiting growth of USP test organisms and met USP preservative standards. Manufacturing, (b) (4) procedures, sterility controls, and the container closure system were deemed acceptable by the microbiology reviewer.

4. Non-Clinical Pharmacology Toxicology

The overall recommendation was approvable from a Pharmacology/Toxicology perspective. There are no outstanding pharm tox issues that preclude approval. If approved, the drug would be Pregnancy Category B.

The pharmacodynamic activity of alcaftadine in relation to its proposed indication was examined in antiallergic models in mice and rabbits, mast cell stabilization assays, assays measuring conjunctival epithelial integrity, vascular leak assays, and in assays measuring early and late phase inflammation. Secondary pharmacodynamic studies evaluating the histamine blocking activities of alcaftadine were conducted in rats, guinea pigs, and dogs. In addition, a melanin binding study was negative.

Safety pharmacology studies examined central nervous system activity in rats and cardiovascular and behavioral activity in dogs. In one study, significant shortening of the PQ interval on EKG was observed in dogs receiving repeated dosing with higher mg/kg doses. As the exposure values for these high doses were much higher that those expected following daily ocular administration of the 0.25% ophthalmic solution in humans, PQ interval shortening was not deemed by the reviewer to be an expected consequence of ocular administration in humans. Based on repeated dose toxicology studies in animals,

the reviewer concluded that daily ocular administration of the 0.25% ophthalmic solution does not appear to pose a major concern for ocular or systemic toxicity.

Studies suggested a low potential for drug-drug interactions based on protein binding. There was minimal metabolism by CYP-450 enzymes.

The genetic toxicity of alcaftadine was examined in a full panel of *in vitro* and *in vivo* genetic toxicology assays. The reviewer assessed the studies as indicating minimal genotoxicity potential for the drug.

The applicant requested a waiver of carcinogenicity studies in an IND amendment. The request was granted based on: negative mutagenicity results, an expectation of intermittent clinical dosing, low carcinogenicity potential for the antihistamine class as a whole, a lack of carcinogenicity concerns based on structure-activity analysis, an absence of pre-neoplastic lesions in the oral repeated dose toxicology studies, no indication of long term retention in tissues, and low systemic exposure anticipated with ocular administration.

The reviewer's assessment was that animal studies of reproductive and developmental toxicity indicated that alcaftadine has a low potential to limit male or female fertility, cause fetal toxicity, or produce teratogenicity. The information supports a Pregnancy Category B. The reviewer made several suggestions for labeling to provide more detail regarding Use in Specific Populations: Pregnancy, and Impairment of Fertility.

5. Clinical Pharmacology / Biopharmaceutics

The overall recommendation of the Clinical Pharmacology reviewer was that the clinical pharmacology information provided by the applicant in the NDA is acceptable. There are no outstanding clinical pharmacology issues that preclude approval.

The protein binding of alcaftadine and its active metabolite are 39.2% and 62.7% respectively. The metabolism of alcaftadine is mediated by non –CYP450 cytosolic enzymes to the active carboxylic acid metabolite. As noted in the Pharm-Tox summary, *in vitro* studies showed that neither alcaftadine nor the carboxylic acid metabolite substantially inhibited reactions catalyzed by major CYP450 enzymes.

Following bilateral topical ocular administration of 0.25% alcaftadine ophthalmic solution, the mean plasma C_{MAX} of alcaftadine was approximately 0.06 ng/mL and median T_{MAX} occurred at 15 minutes. Plasma concentrations of alcaftadine were below the lower limit of quantification by 3 hours after dosing. Plasma concentrations of the active metabolite were below the lower limit of quantification by 12 hours after dosing. There was no indication of systemic accumulation or changes in plasma exposure of alcaftadine or the active metabolite following daily topical ocular administration. The elimination half life of the active metabolite is approximately 2 hours following topical ocular administration and the metabolite is primarily excreted in the urine.

6. Clinical/Statistical Efficacy

The Clinical Reviewer and CDTL recommended approval, indicating that the clinical studies in the NDA support the use of alcaftadine ophthalmic solution 0.25% for the prevention of itching associated with allergic conjunctivitis. The Statistical Reviewers recommended approval for the prevention of itching associated with allergic conjunctivitis. I concur with their recommendations.

Conjunctival Antigen Challenge (CAC) Studies 05-003-11, 05-003-13, and 09-003-05:

The efficacy review for this NDA relies upon the results of three double masked, vehicle controlled, CAC studies, 05-003-11, 05-003-13, and 09-003-05, which were similar in design. As discussed under section 9 Pediatrics, these studies were limited to children and adults greater than 10 years of age. Subjects were required to have a positive history of ocular allergies and a positive skin test to cat hair, cat dander, or common pollens within the past 24 months. They had to have a positive bilateral CAC reaction (itching and redness) within 10 minutes of installation of the last titration of allergen at visit 1 and at least two out of three time points at visit 2. Following visits 1 and 2, subjects meeting inclusion/exclusion criteria were randomized at visit 3 and underwent a CAC 15 minutes post installation of study meds and a CAC 16 hours post installation of study meds. Visit 4 took place approximately 14 days after visit 3. At visit 4, subjects underwent a CAC 15 minutes post installation of study meds.

The primary efficacy variables for each of the three CAC studies were: 1) Ocular itching evaluated by the subject at 3, 5, and 7 minutes post challenge (0-4 unit scale allowing half unit increments), and 2) Conjunctival redness evaluated by the investigator at 7, 15, and 20 minutes post challenge. For an indication for the treatment of allergic conjunctivitis based on the results of CAC studies, a demonstration of efficacy is recommended to include evidence of statistical significance and clinical relevance. This evidence is based on a statistical difference in scores for itching or redness between the vehicle and test drug at all time points as well as a minimum difference in mean scores for itching or redness (a difference in scores greater than 0.5 units at all time points with two of three time points demonstrating at least a 1 unit difference in scores). Scores for itching and redness are considered separately. In studies 05-003-11 and 05-003-13, eyes were treated as independent units in the analyses. In study 09-003-05, subjects were the units of analyses after averaging the scores for both eyes.

For Studies 05-003-11 and 05-003-13, subjects were randomized to one of three treatment arms:

- Original formulation of alcaftadine ophthalmic solution administered bilaterally
- Original formulation of alcaftadine ophthalmic solution administered in one eye and vehicle administered in the other eye
- Vehicle ophthalmic solution administered bilaterally

For study 09-003-05, subjects were randomized to one of two treatment arms:

- New formulation of alcaftadine ophthalmic solution administered bilaterally
- Vehicle ophthalmic solution administered bilaterally

A comparison of differences for ocular itching scores for each of the 3 studies is shown in the table below from page 8 of the CDTL review for NDA 22-134:

Comparison of Differences for Ocular Itching[a] Scores (ITT Population)			
Visit Time Point	Protocol 05-003-11 (Vehicle N=130[b]) (Alcaftadine N=122[b]) **Difference[d] p-Value[e]**	Protocol 09-003-05 (Vehicle N=30[c]) (Alcaftadine N=30[c]) **Difference[d] p-Value[e]**	Protocol 05-003-13 (Vehicle N=87[b]) (Alcaftadine N=89[b]) **Difference[d] p-Value[e]**
Visit 3 (16 hours post dose)			
3 Min. Post-Challenge	-0.865 (p<0.001)	-1.731 (p<0.001)	-1.094 (p<0.001)
5 Min. Post-Challenge	-0.963 (p<0.001)	-1.687 (p<0.001)	-1.219 (p<0.001)
7 Min. Post-Challenge	-0.957 (p<0.001)	-1.576 (p<0.001)	-1.109 (p<0.001)
Visit 4 (15 min post dose)			
3 Min. Post-Challenge	-1.345 (p<0.001)	-1.500 (p<0.001)	-1.321 (p<0.001)
5 Min. Post-Challenge	-1.319 (p<0.001)	-1.491 (p<0.001)	-1.255 (p<0.001)
7 Min. Post-Challenge	-1.240 (p<0.001)	-1.474 (p<0.001)	-1.170 (p<0.001)

[a] Ocular itching evaluated on a 0 to 4 scale, allowing for half increment scores, where 0 indicates no itching and 4 indicates severe itching.
[b] N represents the number of eyes treated.
[c] N represents the number of subjects treated, all patients treated bilaterally.
[d] Difference = mean of Alcaftadine minus mean of vehicle; a negative difference favors Alcaftadine.
[e] p-Value based on Wilcoxon Rank Sum Test for comparing Alcaftadine to vehicle.

With the exception of the 16 hours post dose CAC in protocol 05-003-11, a statistically robust difference in ocular itching scores was achieved at all points in addition to a difference in mean itching scores of greater than 1 unit at all time points. CACs conducted 16 hours post study medication instillation at Visit 3 (to assess duration of action) and 15 minutes post study medication instillation at Visit 4 (to assess onset of action) were consistent.

For conjunctival redness scores, all three studies failed to demonstrate clinical relevance although a statistically significant difference in redness scores was apparent at most time points.

Issues concerning multiplicity and correlated data in the analyses of these studies were discussed by the Statistical Reviewer. Multiplicity problems arise when individual components of a co-primary endpoint are intended as separate claims (in this case prevention of itching and prevention of redness). To adjust for multiplicity, each endpoint should be tested at a significance level of 2.5% (two-sided) to control the overall Type I error at the desired level of 5%. In these studies, the treatment comparisons with respect to the ocular itching score had p values of <0.001 at all post-allergen challenge time points at Visits 3 and 4. Thus the results are significant at a two-sided significance level of 2.5%. The ocular itching scores for the right eye and left eye

of the same subject are expected to be correlated, and the eye was the unit of analysis for studies 05-003-11 and 05-003-13. For each of the studies, repeated measures for each subject were carried out. The Statistical Reviewer addressed this by performing a repeated measure analysis using an unstructured correlation structure. The overall results of the repeated measure analysis were consistent with the primary analysis for each study.

Environmental Efficacy and Safety Trial 06-003-009:

Subjects > 10 years of age with a positive diagnostic test for ragweed within the past 2 years or a positive bilateral ocular response to ragweed induced in a manner similar to the CAC studies were enrolled and randomized to one of three arms: Vehicle, Alcaftadine (modified formulation), or Olopatadine. They were followed for 6 weeks with 3 follow-up study visits and 3 follow-up phone contacts. The primary efficacy variables were average daily evening ocular itching and redness scores based on daily diary calculated during the 14 consecutive days of peak pollen. A total of 365 subjects were randomized (72 Vehicle, 147 Alcaftadine, and 146 Olopatadine). This study failed its primary endpoints. Per the Clinical Reviewer, of the 365 subjects enrolled, 100 subjects had all "0" scores for ocular diary itching data during the 14 day peak pollen duration, and 60 subjects had all "0" scores for ocular redness during the 14 day peak pollen duration. Thus, both the Clinical Reviewer and CDTL concluded that it would be difficult to demonstrate a treatment effect. I concur with this conclusion. These subjects are included in the safety data based discussed in Section 7.

7. Safety

The Clinical Reviewer concluded that alcaftadine ophthalmic solution 0.25% demonstrated an acceptable safety profile. The CDTL concluded that there is substantial evidence of safety consisting of adequate and well controlled studies which demonstrate that alcaftadine ophthalmic solution 0.25%, dosed once a day, is safe for the prevention of itching associated with allergic conjunctivitis. I concur with their conclusions.

The safety data base includes two 6 week studies: Study 06-003-09, an environmental trial in subjects age 10 years and older using the modified formulation of alcaftadine in one of the three study arms (described in Section 6 above), and Study 05-003-10.

Safety Study 05-003-10:
Study 05-003-10 had the primary objective of evaluating the safety of alcaftadine ophthalmic solution over a 6 week period. The study enrolled 909 healthy volunteers age 3 years and above, with 852 subjects completing the study. Subjects were randomized using a 2:1 ratio to the original formulation of alcaftadine or vehicle and instilled a single drop of study drug in both eyes once daily for 6 weeks.

The safety data base also included the three CAC studies in which the subjects were exposed to the drug for two days (these studies are described in Section 6 above).

A total of 756 subjects were exposed to alcaftadine ophthalmic solution 0.25% for 6

weeks. A total of 171 subjects participating in the CAC studies were exposed to alcaftadine ophthalmic solution 0.25% for two days.

No deaths were reported in any clinical trial during development. There were 5 subjects who received alcaftadine ophthalmic solution 0.25% who experienced a serious adverse event; none of these were considered to be related to the study medication. Dropouts and withdrawals were similar among treatment groups, however, there seemed to be more withdrawals in the alcaftadine arms attributed to eye redness, eye irritation, or conjunctivitis. Treatment emergent adverse events with an incidence $\geq$ 1% which seemed more common among subjects receiving alcaftadine included: application site pruritis, eye irritation, eye pruritis, eye redness, instillation site burning, instillation site stinging, and nasopharyngitis.

Study 05-003-10 enrolled 34 subjects > 64 years of age. There was no clinically significant difference in AE profile comparing subjects > 64 years of age with younger patients. Study 01-003-10 enrolled pediatric subjects 3 years of age and older, and study 06-003-09 enrolled pediatric subjects 10 years of age and older. There were no unexpected safety concerns observed in pediatric subjects.

While study 05-003-10 tested the original formulation of the product, study 06-003-09 provided safety data for 6 week use of the modified formulation of the product. The safety findings of study 06-003-09 did not differ from the safety findings of study 05-003-10.

Common side effects seen with this class of medications include: headache, asthenia, blurry vision, eye burning/stinging upon installation, eye pain, cold/flu symptoms, cough, fatigue, dry eye, foreign body sensation, lid edema, keratitis, hyperemia, nausea, pharyngitis, pruritis, rhinitis, sinusitis, sore throat, and taste perversion/bitter taste. As noted above, many of these common side effects were observed in the alcaftadine clinical trials.

8. Advisory Committee Meeting

NDA 22-134 was not referred to an advisory committee for the following reasons: 1) There are a number of other approved ophthalmic products in this class of drugs with this indication. 2) Evaluation of the safety data did not reveal particular safety concerns that were unexpected for the antihistamine class with topical ophthalmic use. 3) The design and results of the efficacy trials did not pose particular concerns.

9. Pediatrics

At an EOP2 meeting with the applicant on Feb. 1, 2005, it was agreed that subjects aged 3 years and above would be included in a multi-center safety study (05-003-10). While allergic conjunctivitis commonly occurs in children, it was also agreed that children less than 10 years of age cannot reliably describe the subjective endpoint of itching, the disease is quite similar in children and adults, and there are not age related differences

which would be expected to affect safety or efficacy . Therefore, the efficacy data established in those age 10 years and older can be extrapolated down to 2 years of age.

10. Other Relevant Regulatory Issues

The inspections of two clinical research sites, the sponsor, and a CRO were summarized by the DSI Reviewer. Three sites received a final classification of NAI and the reviewer recommended that the data be considered reliable. The Sponsor inspection found that the sponsor's drug reconciliation documentation did not indicate that all bottles of study drug packed, shipped, and used in the study were accounted for in the return and destruction of the product. In addition, there was inadequate documentation of the disposition of study drug not shipped to sites. The final classification based on the inspection report was VAI. The DSI reviewer concluded that the regulatory violations noted would not affect subject safety or data integrity. Therefore, the data should be considered reliable.

Financial Disclosure forms were reviewed by the Clinical Reviewer. There were no principal investigators with proprietary interest or any significant interest in the tested product.

There are no other unresolved relevant regulatory issues.

11. Labeling

Following the review of several proposed proprietary names that were deemed subject to confusion with other marketed products, The DMEPA Proprietary Name Risk Assessment findings indicate that the proposed name, Lastacaft, is not vulnerable to name confusion that could lead to medication errors, nor is it considered promotional. Thus, DMEPA had no objection to the proposed proprietary name, Lastacaft, for this product.

The DMEPA reviewer raised concern regarding the colors chosen for the carton and container labeling as green and yellow correspond with miotic and beta blocker ophthalmic medications. The CDTL reviewer clarified that the American Academy of Ophthalmology recommendations for cap color corresponding to drug class are not meant to preclude the use of colors on the carton or container labeling.

The DDMAC and SEALD reviewers made a number of labeling recommendations. The approved labeling reflects many of these recommendations. The reviewers recommended that additional detail concerning clinical trials be added to the Adverse Events and Clinical Studies sections of the label (for example, more detail regarding clinical trials and identifying adverse reactions that resulted in a significant rate of discontinuation or other clinical interventions). The CDTL indicated that there were no adverse events that resulted in a significant rate of discontinuation. Although brief, there is information regarding the clinical trials in the Clinical Studies section of the approved labeling. The approved labeling is consistent with labeling for other products in this class with this indication which relied upon CAC studies to demonstrate efficacy.

12. Decision/Action/Risk Benefit Assessment

I concur with the review team, CDTL, and Division Director that alcaftadine ophthalmic solution 0.25% should be approved for the proposed indication.

Substantial evidence of efficacy for the proposed indication of the prevention of itching associated with allergic conjunctivitis has been demonstrated in the 3 CAC studies, which were adequate and well controlled. The safety data base included 2 studies with 6 weeks exposure to the product. Adverse effects did not result in a significant rate of discontinuation in clinical trials and were those anticipated with topical ophthalmic antihistamine application. Thus, the risk benefit assessment is favorable.

There are no recommendations for Post-marketing Risk Evaluation and Mitigation Strategies.

There are no recommendations for Postmarketing Requirements and Commitments.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22134	ORIG-1	VISTAKON PHARMACEUTICALS LLC	Lastacaft (alcaftadine ophthalmic solution) 0.25%

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

/s/

JOHN J FARLEY
07/28/2010

EDWARD M COX
07/28/2010