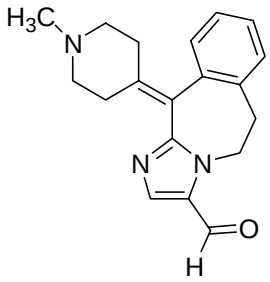
Cross-Discipline Team Leader Review for NDA 22-134

Date	June 22, 2010
From	William M. Boyd, M.D.
Subject	Cross-Discipline Team Leader Review
NDA #	22-134
Applicant	Vistakon Pharmaceuticals, LLC
Date of Submission	September 29, 2009
PDUFA Goal Date	July 29, 2010
Type of Application	505(b)(1)
Name	Lastacaft (alcaftadine ophthalmic solution) 0.25%
Dosage forms / Strength	Topical ophthalmic solution
Proposed Indication(s)	Indicated for the prevention of itching associated with allergic conjunctivitis
Recommended:	Recommended for Approval

1. Introduction



Chemical Name: 6,11-dihydro-11-(1-methyl-4-piperidinylidene)-5*H*-imidazo[2,1-b] [3] benzazepine-3-carboxaldehyde

Lastacaft (alcaftadine ophthalmic solution) 0.25% is a H1 histamine antagonist and inhibitor of the release of histamine from mast cells.

There is no previous marketing experience with Lastacaft (alcaftadine ophthalmic solution) 0.25% as the proposed active ingredient has not been previously approved in the United States or abroad.

Throughout this review, alcaftadine ophthalmic solution 0.25% may alternately be referred to as Lastacaft, (b) (4) or R89674.

2. Background

The efficacy endpoints chosen for the phase 3 studies have been widely used in clinical studies of ophthalmic solutions and are recognized as reliable, accurate, and relevant for evaluation of the efficacy and safety of investigational products. For an indication for the treatment of allergic conjunctivitis, a demonstration of efficacy is recommeded to include evidence of statistical

significance and clinical relevance in the resolution of both ocular itching and redness. In the case of antigen challenge studies or controlled environmental studies, the difference between groups is recommended to be at least one unit on a scale from zero to four.

Table of Currently Available Treatments for Proposed Indication of Itching Associated with Allergic Conjunctivitis

Brand Name	Name of Drug	NDA
Alocril	nedocromil	21-009
Acular	ketorolac	19-700
Optivar	azelastine	21-127
Alamast	pemirolast	21-079
Pataday	olopatanol	21-545
Elestat	epinastine	21-565
Bepreve	bepotastine besilate	22-288

Adverse events for this class of drugs (topical H_1 antagonists) are well known. Common side effects seen with this class include: headache, asthenia, blurry vision, eye burning/stinging upon instillation, eye pain, cold/flu symptoms, cough, fatigue, dry eye, foreign body sensation, lid edema, keratitis, hyperemia, nausea, pharyngitis, pruritus, rhinitis, sinusitis, sore throat, and taste perversion/bitter taste.

A summary of the clinical studies forming the basis for approval for NDA 22-134 are:

ORIGINAL FORMULATION				
Formulation	**Study #**	**Study Design**	**Age**	**Comments**
#PD – F-3730	05-003-10	Safety	3+	No serious adverse events
#PD – F-3730	05-003-11	Efficacy – CAC*	10+	Successful**
#PD – F-3730	05-003-13	Efficacy – CAC*	10+	Successful**
MODIFIED FORMULATION				
Formulation	**Study #**	**Study Design**	**Age**	**Comments**
#PD – F-5525-2	06-003-09	Efficacy - Environmental	10+	FAILED (for both ocular itching and redness)
#PD – F-5525-2	09-003-05	Efficacy – CAC*	10+	Successful**

* CAC – Conjunctival antigen challenge study
**NOTE: Failed for ocular redness; Successful for itching

Studies 05-003-10, 05-003-11 and 05-003-13 were performed with the original formulation

(#PD-F-3730). Study 05-003-10 was a safety trial in normal volunteers that included ages from 3 and above.

Studies 05-003-11 and 05-003-13 were efficacy trials using the CAC (Conjunctival Antigen Challenge) study model. Studies 05-003-11 and 05-003-13 included subjects age > 10; it was agreed that subjects less than 10 years old can not reliably describe the subjective endpoint of itching. These trials were successful for itching but failed for ocular redness.

After having performed the above three studies (05-003-10, 05-003-11 and 05-003-13) the drug formulation was modified to include a reduction in the buffer concentration, preservative and chelating agent, that were made to improve overall comfort of the product. With the change in formulation the agency requested an additional efficacy trial to support this change. Study 06-003-09 was an environmental study with the modified formulation.

The environmental study 06-003-09 enrolled a total of 365 subjects with a history of seasonal allergic conjunctivitis. Many of the subjects enrolled exhibited no itching or redness during the course of the study, making it impossible to demonstrate a treatment effect; one-hundred (100) subjects had all "0" scores for ocular diary itching data and sixty (60) subjects had all "0" scores for ocular redness data during the 14-day peak pollen duration. Environmental study 06-003-09 failed both its endpoints of ocular itching and ocular redness.

It is not uncommon for environmental studies to fail for seasonal allergic conjunctivitis. As demonstrated in Study 06-003-09, many subjects may not illicit a response to the seasonal allergen, making it impossible to demonstrate any change in ocular itching or redness. Subjects may avoid exposure to the allergen by staying inside, or avoiding those areas in season where the allergen may be present.

After the failed environmental trial a Conjunctival Antigen Challenge (CAC) study (09-003-05) was performed with the modified formulation to demonstrate its efficacy. Using the CAC study, 09-003-05 was successful for its efficacy endpoint of ocular itching, though it failed for ocular redness.

3. CMC

From the two CMC Reviews finalized 5/14/2010 and 6/21/2010:

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 by 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 manufacturing processes and controls information for the 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. The facility inspection was cleared by the Office of Compliance on April 23, 2010.

DESCRIPTION AND COMPOSITION OF THE DRUG PRODUCT:

The subject drug product is a sterile ophthalmic solution containing 2.5 mg/mL alcaftadine. The primary packaging configuration consists of a low-density polyethylene (LDPE) bottle, dropper tip, and a polypropylene cap. The proposed commercial packaging configurations include a 5 mL bottle with a 3 mL fill volume (b) (4)) and a sample size utilizing the 5 mL bottle with a 1 mL fill volume (b) (4)). The proposed commercial formulation (PD-F-5525) is provided in the following table.

Components	Concentration (mg/mL)	Function
Alcaftadine	2.5	Active ingredient
Sodium Phosphate Monobasic Monohydrate	(b) (4)	
Edetate Disodium, Dihydrate		
Sodium Chloride		
Benzalkonium Chloride	0.05	Preservative
NaCl and/or HCl	pH adjustment to 7.0 target	pH adjustment
Purified Water	(b) (4)	

PROPOSED SPECIFICATIONS:

(b) (4)

4. Nonclinical Pharmacology/Toxicology

From the original Pharmacology/Toxicology Review finalized 6/2/2010:

Repeated topical ocular administration of R89674 in 14-day and 6-month studies in rabbits did not cause significant systemic or ocular toxicity. The NOEL value for both ocular and systemic toxicity in the 6-month study was considered to be 0.5% TID. After 6-months of dosing, the high dose produced plasma R90692 CMax values of 53.9 (male) and 67.9 (female) ng/ml and AUC(0-t) values of 49.3 (male) and 72.1 (female) ng x hr/ml.

In a 6-month oral repeated-dose study in rats, slight to moderate toxicity occurred at R89674 doses of ≥ 20 mg/kg/day. The liver appeared to be the target organ for toxicity. Liver weights were increased in male and female rats and female liver histopathology included hepatic atrophy and diffuse hyperplasia of oval cells and bile ducts. The NOAEL for this study was considered to be 5 mg/kg/day and R90692 AUC0-t values associated with this dose were 0.627 (male) and 0.493 (female) µg x h/ml.

In a 6-month oral repeated-dose study in dogs, a few toxicological effects occurred in the high-dose group (40 mg/kg/day) including transient salivation, rough haircoat, increased incidences of focal alopecia, decreased body weights and body weight gains, shortened PQ interval, and a slight increase in systolic blood pressure. Some hematological and serum chemistry values were also changed and the NOAEL for this study was considered to be 10 mg/kg/day which was associated with a R90692 AUC0-∞ value of 29.6 µg x h/ml.

R89674 was negative for mutagenicity and did not increase chromosome aberrations in a full panel of genetic toxicology assays including the Ames test, a chromosome aberration assay, a thymidine kinase mutation assay, and two mouse micronucleous assays. R90692 also did not increase mutations in an Ames test. A waiver for carcinogenicity studies was granted.

In a Segment I reproductive toxicity study in rats, R89674 did not cause adverse fertility effects at doses of ≤ 60 mg/kg/day in males and ≤ 20 mg/kg/day in females. In Segment II studies in rats and rabbits, female fertility was not impaired, no teratogenic effects occurred, and maternal lethality did not occur at doses ≤ 20 mg/kg/day in rats or doses ≤ 80 mg/kg/day in rabbits. In a Segment III study in rats, the NOAEL for maternal toxicity was considered to be 20 mg/kg/day, but the reproductive NOEL was considered to be 30 mg/kg/day as no adverse effects on F0 reproduction occurred. The NOAEL for offspring viability and growth was 5 mg/kg/day.

In both the 14-day and 6-month repeated-dose ocular studies in rabbits, no ocular or systemic toxicity occurred, and the NOEL values were the highest administered doses of 0.5% R89674/eye TID. In the 6-month rat and dog oral repeated-dose toxicology studies where some R89674-related changes in hematological and clinical chemistry did occur as well as histopathology of the liver in rat, the exposure levels associated with the NOAEL doses were much higher. The R90692 AUC values corresponding to the NOAEL doses in the 6-month rat and dog studies provide margins of exposure of 40 and 22 for male and female rats respectively and 2789 for dogs relative to the clinical R90692 $AUC_{0\text{-last}}$ of 10.613 ng x h/mL in the clinical pharmacokinetic protocol # 05-003-09.

5. Clinical Pharmacology/Biopharmaceutics

From the original Clinical Pharmacology Review finalized 5/28/2010:

The protein binding of alcaftadine and the 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. *In vitro* studies showed that neither alcaftadine nor the carboxylic acid metabolite substantially inhibited reactions catalyzed by major CYP450 enzymes. Thus, clinically relevant interactions based on inhibition of CYP450 enzymes are not to be expected for Alcaftadine and concomitantly administered drugs.

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 the median T_{max} occurred at 15 minutes. Plasma concentrations of alcaftadine were below the lower limit of quantification (0.01 ng/mL) by 3 hours after dosing. The mean C_{max} of the active metabolite was approximately 3 ng/mL and occurred at 1 hour after dosing. Plasma concentrations of the active metabolite were below the lower limit of quantification (0.10 ng/mL) 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 hr following topical ocular administration and the metabolite is primarily eliminated unchanged in the urine.

6. Sterility Assurance

From the original Product Quality Microbiology Review finalized 6/22/2010:

There are no microbiology deficiencies identified.

The proposed commercial drug product, Alcaftadine 2.5 mg/mL ophthalmic solution (formulation PD-F-5525) is adequately preserved with 0.05 mg/mL (0.005% w/w) benzalkonium chloride. In addition, it also has (b) (4)

According to Report MI-R-5655-1, decreasing levels of benzalkonium chloride and EDTA a (b) (4) (b) (4) were prepared in lab batches R089674-AAA and were subject to Antimicrobial Effectiveness Test (AET) against USP indicator organisms: *Pseudomonas aeruginosa, Escherichia coli, Staphylococcus aureus, Candida albicans and Aspergillus niger*. The formulation was effective against the USP test organisms and met USP preservative efficacy requirements as seen Tables 2a, 2b, & 2c (copied from Report MI-R-5655-1). The antimicrobial effectiveness was also maintained and met USP requirements at lower levels of the preservative, (b) (4) mg/mL or (b) (4)% w/w.

Primary packaging components are sterilized by (b) (4) at (b) (4), a contract sterilization facility. The primary packaging components are manufactured as follows:

- Bottles: (b) (4)
- Dropper Tips: (b) (4)
- Caps: (b) (4)

(b) (4)

Based on the teleconference on January 22, 2010 with the FDA, the Sponsor has implemented Bacterial Endotoxins release specification for the topical ophthalmic product. The test will be performed according to USP <85> *Bacterial Endotoxins Test* with product release specification at (b) (4) EU/mL. Bacterial endotoxins test will be performed using a Limulus Amebocyte Lysate (LAL) test by gel-clot method. Inhibition and enhancement testing of the product demonstrated acceptable results at a dilution of (b) (4) EU/mL for all six stability lots. An endotoxin limit of (b) (4) EU/mL is requested as the final release specification because the drug product is intended to be used on the ocular surface as a topical with an intact cornea and not intraocularly.

7. Clinical/Statistical - Efficacy

From the original Medical Officer Review dated 7/22/2010:

Analyses of Endpoints – Itching and Redness

Conjunctival Antigen Challenge

The primary efficacy variables for CAC Studies Protocol 05-003-11, Protocol 05-003-13 and 09-003-05 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 (0-4 unit scale, allowing half unit increments)

Comparison of Differences for Ocular Itching[a] Scores			
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.

In all three efficacy studies (Protocols 05-003-11, 09-003-5, and 05-003-13), treatment with alcaftadine ophthalmic solution once daily led to less ocular itching compared with Vehicle (placebo)-treated eyes when CAC was conducted 16 hours post study medication instillation at Visit 3 to assess duration of action (above Table), and 15 minutes post study medication instillation at Visit 4 to assess onset of action (above Table). With one exception, a difference of ~1 unit or greater in the mean ocular itching score was achieved for eyes treated with alcaftadine ophthalmic solution once daily compared with Vehicle (placebo)-treated eyes at all post allergen challenge time points at Visit 3 and Visit 4 in all four studies. The exception was the 3-minute post allergen challenge time point at Visit 3 in Protocol 05-003-11, where a difference of -0.865 in the mean ocular itching score was achieved.

To establish efficacy for itching of alcaftadine ophthalmic solution over Vehicle, ocular itching mean difference scores (active minus vehicle-treated eye) of greater than 1 unit for at least two of three time points would be necessary.

The results from the three efficacy trials (Protocols 05-003-11, 09-003-5, and 05-003-13), demonstrate a statistically significant and clinically relevant difference between alcaftadine ophthalmic solution and vehicle for the prevention of ocular itching associated with allergic conjunctivitis.

Comparison of Differences for Conjunctival Redness[a] Scores			
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)			
7 Min. Post-Challenge	-0.410 (p<0.001)	-0.952 (p<0.001)	-0.369 (p=0.006)
15 Min. Post-Challenge	-0.398 (p =0.002)	-0.542 (p=0.009)	-0.243 (p=0.054)
20 Min. Post-Challenge	-0.372 (p=0.003)	-0.542 (p=0.005)	-0.184 (p=0.131)
Visit 4 (15 min. post dose)			
7 Min. Post-Challenge	-0.797 (p<0.001)	-0.879 (p<0.001)	-0.526 (p<0.001)
15 Min. Post-Challenge	-0.696 (p<0.001)	-0.612 (p=0.007)	-0.139 (p=0.173)
20 Min. Post-Challenge	-0.585 (p<0.001)	-0.578 (p=0.011)	-0.092 (p=0.311)

[a] Conjunctival redness 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.
[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.

For conjunctival redness assessment, the pre-specified criteria of achieving mean difference scores (active minus Vehicle [placebo]-treated eye) of greater than 0.5 units differences at all time points, with two of three time points demonstrating at least 1 unit difference, was not accomplished in the Phase 3 CAC studies. Therefore, although statistical significance was noted at most time points, Alcaftadine ophthalmic solution was unable to clearly demonstrate clinical significance compared to Vehicle (placebo) in preventing conjunctival redness in the three efficacy studies (Protocols 05-003-11, 09-003-5, and 05-003-13).

To establish efficacy for conjunctival redness of alcaftadine ophthalmic solution over Vehicle, mean difference scores (active minus vehicle-treated eye) of greater than 0.5 unit at all time points, with two of three time points demonstrating at least a 1 unit difference for conjunctival redness would be necessary.

The results from the three efficacy trials (Protocols 05-003-11, 09-003-5, and 05-003-13), did not demonstrate a clinically significant difference between alcaftadine ophthalmic solution and vehicle for the prevention of conjunctival redness associated with allergic conjunctivitis.

Environmental Study

The primary objective for Environmental Study Protocol 06-003-009 was to evaluate ocular itching and conjunctival redness. The primary efficacy variables for Environmental Study Protocol 06-003-09 were Diary Data (graded by subjects):

- Average* of daily evening ocular itching score
- Average* of daily evening ocular redness score

* Calculated based on data collected during the 14 consecutive days of peak pollen.

Of the 365 subjects enrolled, one-hundred (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 data during the 14-day peak pollen duration. Many of the subjects exhibited no itching at all during the course of the study, making it difficult to show a treatment effect.

Efficacy Summary Statement

There is substantial evidence of effectiveness consisting of adequate and well controlled studies which demonstrate that patients receiving alcaftadine ophthalmic solution 0.25% experienced a statistically and clinically significant response in the reduction of ocular itching. The data support alcaftadine ophthalmic solution 0.25% administered once a day for the prevention of itching associated with allergic conjunctivitis.

There is **not** substantial evidence that patients receiving alcaftadine ophthalmic solution 0.25% experienced a clinically significant response in the reduction of ocular redness. The data does **not** support alcaftadine ophthalmic solution 0.25% administered once a day for the prevention of redness associated with allergic conjunctivitis.

8. Safety

From the original Medical Officer Review dated 7/22/2010:

The safety data base includes two 6 week studies: Study 06-003-09, an environmental trial in subjects aged 10 and older, and Study 05-003-10, a study in normal volunteers aged 3 and older. These two studies are Group 1 in the Adverse Event data.

The three CAC studies (05-003-11, 05-003-13 and 09-003-05), where the subjects were exposed to the drug for two days, provide additional supportive safety data. These three studies are Group 2 in the Adverse Event data.

Group 1 (Studies 05-003-10 and 06-003-09) and Group 2 (05-003-11, 05-003-13 and 09-003-05) are both used to support product labeling.

Overall Exposure at Appropriate Doses/Durations

Extent of Once Daily Exposure by Study			
Number of Subjects (Number of Eyes Treated)/(Median Range) Extent of Exposure			
Study	**Alcaftadine ophthalmic solution 0.25%**	**Inactive Control Only[a]**	**Active Control Only[b]**
Group 1: 6 week studies 05-003-10 and 06-003-09			
05-003-10	N=609 (2 eyes) 43 (1-52) days	N=300 (2 eyes) 43 (1-51) days	
06-003-09	N=147 (2 eyes) 43 (1-49) days	N=72 (2 eyes) 43 (8-46) days	N=1469 (2 eyes) 43 (1-51) days
Group 2. CAC studies 05-003-11, 05-003-13 and 09-003-05			
05-003-11	N=42 (1 eye) N=40 (2 eyes) 2 (1-2) days	N=44 (2 eyes) 2 (2-2) days	
05-003-13	N=29 (1 eye) N=30 (2 eyes) 2 (1-2) days	N=29 (2 eyes) 2 (2-2) days	
09-003-05 (Modified Formulation of alcaftadine)	N=30 (2 eyes) 2 (1-2) days	N=30 (2 eyes) 2 (1-2) days	

[a] Vehicle ophthalmic solution
[b] Patanol (0.1%)

Study 05-003-10 Study Completion								
	Treatment Group							
	Vehicle				**Alcaftadine 0.25%**			
	≤ 17 y (N=37) n (%)	18-64 y (N=252) n (%)	> 64 y (N=11) n (%)	All ages (N=300) N (%)	≤ 17 y (N=77) n (%)	18-64 y (N=509) n (%)	> 64 y (N=23) n (%)	All ages (N=609) n (%)
Randomized	37 (100)	252 (100)	11 (100)	300 (100)	77 (100)	509 (100)	23 (100)	609 (100)
Safety Population	37 (100)	252 (100)	11 (100)	300 (100)	77 (100)	509 (100)	23 (100)	609 (100)
Completed	37 (100)	238 (94)	10 (91)	285 (95)	74 (96)	472 (93)	21 (91)	567 (93)

Study 06-003-09 Study Completion				
	Treatment Group			
	Vehicle Combined (N=72) n (%)	Alcaftadine 0.25% (N=147) n (%)	Patanol (N=146) n (%)	Total (N=365) n (%)
Randomized	72 (100)	147 (100)	146 (100)	365 (100)
Safety population	72 (100)	147 (100)	146 (100)	365 (100)
Completed	68 (94)	140 (95)	138 (94)	346 (95)

The two 6 week trials provided adequate exposure to assess the safety profile of alcaftadine ophthalmic solution 0.25%.

Subject Disposition

Study 05-003-10: Subject Disposition

Study 05-003-10 Study Completion								
	Treatment Group							
	Vehicle				Alcaftadine 0.25%			
	≤ 17 y (N=37) n (%)	18-64 y (N=252) n (%)	> 64 y (N=11) n (%)	All ages (N=300) N (%)	≤ 17 y (N=77) n (%)	18-64 y (N=509) n (%)	> 64 y (N=23) n (%)	All ages (N=609) n (%)
Randomized	37 (100)	252 (100)	11 (100)	300 (100)	77 (100)	509 (100)	23 (100)	609 (100)
Safety Population	37 (100)	252 (100)	11 (100)	300 (100)	77 (100)	509 (100)	23 (100)	609 (100)
Completed	37 (100)	238 (94)	10 (91)	285 (95)	74 (96)	472 (93)	21 (91)	567 (93)
Discontinued	0	14 (6)	1 (9)	15 (5)	3 (4)	37 (7)	2 (9)	42 (7)
Reasons								
Subject Choice	0	4 (1.6)	0	4 (1.3)	0	4 (0.8)	0	4 (0.7)
Lost to Follow-up	0	1 (0.4)	0	1 (0.3)	0	5 (1.0)	0	5 (0.8)
Adverse Event	0	8 (3.2)	0	8 (2.7)	1 (1.3)	20 (3.9)	2 (8.7)	23 (3.8)
Other[a]	0	1 (0.4)	1 (9.1)	2 (0.7)	2 (2.6)	8 (1.6)	0	10 (1.6)

[a] Other reasons included noncompliance with per-protocol visit schedule, protocol violation, lost study medication and sponsor/medical monitor decision.

In study 05-003-10 discontinuations due to Adverse Events occurred in approximately 3% of subjects with 27 in the drug treatment group and seven in the vehicle group listed below:

Study 05-003-10: Patient Withdrawals Due to Adverse Events

Subject Number	Treatment Group	AE Leading to Discontinuation
20011	Alcaftadine	Urticaria
30068	Alcaftadine	Eye redness
30079	Alcaftadine	Eye redness/irritation, photophobia, xeropthalmia
30093	Alcaftadine	Dysgeusia, oral pain
30101	Alcaftadine	Eye redness
30110	Alcaftadine	Eye redness, lacrimation, photophobia
30144	Alcaftadine	Allergic conjunctivitis
30167	Alcaftadine	Eye redness, xeropthalmia
30181	Alcaftadine	Eye redness
30188	Alcaftadine	Eye irritation, instillation site burning
30189	Alcaftadine	Bacterial conjunctivitis, allergic conjunctivitis
30229	Alcaftadine	Eye redness, lacrimation increased
30250	Alcaftadine	Abnormal eye sensation, vision blurred, dysgeusia, headache, sinus pain
30333	Alcaftadine	Conjunctivitis
30420	Alcaftadine	Conjunctivitis
30430	Alcaftadine	Conjunctivitis

30505	Alcaftadine	Eye redness/pruritus
30524	Alcaftadine	Eye redness/pruritus
30551	Alcaftadine	Hypertension
30577	Alcaftadine	Eye redness
30643	Alcaftadine	Drug Abuser
30685	Alcaftadine	Eyelid edema, urticaria
30715	Alcaftadine	Nasopharyngitis
30121	Vehicle	Conjunctival Hyperemia
30241	Vehicle	Asthma
30408	Vehicle	Hypercholesterolemia, hypertension
30470	Vehicle	Ocular discomfort, macular hole
30480	Vehicle	Eye redness
30550	Vehicle	Eye redness
30680	Vehicle	Nasopharyngitis
30714	Vehicle	Nasopharyngitis

Study 06-003-09: Subject Disposition

Study 06-003-09 Study Completion				
	Treatment Group			
	Vehicle Combined (N=72) n (%)	Alcaftadine 0.25% (N=147) n (%)	Patanol (N=146) N (%)	Total (N=365) N (%)
Randomized	72 (100)	147 (100)	146 (100)	365 (100)
Safety population	72 (100)	147 (100)	146 (100)	365 (100)
Completed	68 (94.4)	140 (95.2)	138 (94.5)	346 (94.8)
Discontinued	4 (5.6)	7 (4.8)	8 (5.5)	19 (5.2)
Reasons				
Subject Choice	1 (1.4)	1 (0.7)	2 (1.4)	4 (1.1)
Lost to Follow-up	0	4 (2.7)	2 (1.4)	6 (1.6)
Adverse Event	3 (4.2)	2 (1.4)	1 (0.7)	6 (1.6)
Other	0	0	3 (2.1)	3 (0.8)

[a] Other reasons included noncompliance with per-protocol visit schedule, protocol violation, lost study medication and sponsor/medical monitor decision.

In study 06-003-19 discontinuations due to Adverse Events occurred in 7 subjects; 2 in the drug treatment group, 1 in the Patanol group and three in the vehicle group. The discontinuations due to Adverse Events are listed below:

Study 06-003-09: Patient Withdrawals Due to Adverse Events

Subject Number	**Treatment Group**	**AE Leading to Discontinuation**
60004	Alcaftadine	Eye redness/pruritus
60131	Alcaftadine	Hypersomnia, irritability
60051	Patanol	Dysgeusia
60032	Vehicle	Herpes Zoster
60021	Vehicle	Ear infection
60271	Vehicle	Bronchitis, pyrexia

Studies 05-003-11 and 05-003-13: Subject Disposition

	05-003-11			05-003-13			Pooled		
	Vehicle/ Vehicle n (%)	Vehicle/ Alcaftadine n (%)	Alcaftadine/ Alcaftadine n (%)	Vehicle/ Vehicle n (%)	Vehicle/ Alcaftadine n (%)	Alcaftadine/ Alcaftadine n (%)	Vehicle/ Vehicle n (%)	Vehicle/ Alcaftadine n (%)	Alcaftadine/ Alcaftadine n (%)
Randomized	44 (100)	42 (100)	40 (100)	29 (100)	29 (100)	30 (100)	73(100)	71 (100)	70 (100)
Safety population	44 (100)	42 (100)	40 (100)	29 (100)	29 (100)	30 (100)	73 (100)	71 (100)	70 (100)
Completed	44 (100)	39 (93)	40 (100)	29 (100)	28 (97)	30 (100)	73 (100)	67 (94)	70 (100)
Discontinued	0	3 (7)	0	0	1 (3)	0	0	4 (6)	0
Reasons									
Subject Choice	0	2 (5)	0	0	0	0	0	2 (3)	0
Adverse Event	0	0	0	0	1 (3)	0	0	1 (1)	0
Other[a]		1						1	

[a] Screening failure due to inclusion criteria

In studies 05-003-11 and 05-003-13 there was only 1 discontinuation due to an Adverse Event:

Studies 05-003-11 and 05-003-13: Patient Withdrawals Due to Adverse Events

Subject Number	Treatment Group	AE Leading to Discontinuation
40027	Vehicle/Alcaftadine	Eye redness/pruritus

Study 09-003-05: Subject Disposition

	Vehicle (N=60) n (%)	Alcaftadine (N=60) n (%)
Randomized	30 (100)	30 (100)
Safety population	30 (100)	30 (100)
Completed	29 (96.7)	29 (96.7)
Discontinued	1 (3.3)	1 (3.3)
Reasons		
Subject Choice	1 (3.3)	0
Adverse Event	0	1 (3.3)
Lost to Follow-up	0	0

Studies 09-003-05: Patient Withdrawals Due to Adverse Events

Subject Number	Treatment Group	AE Leading to Discontinuation
01016	Alcaftadine	Goiter

Adverse Events

Incidence ≥ 1 % Treatment-Emergent[a] Adverse Events (TEAE) by Preferred Term and Treatment (Safety Population)

Preferred Term[bc]	Vehicle n (%)	Alcaftadine n (%)	Patanol® n (%)
Group 1	N = 744	N = 1512	N = 292
Application site pruritus	0	4 (0.3)	3 (1.0)
Eye irritation	16 (2.2)	57 (3.8)	1 (0.3)
Eye pruritus	13 (1.7)	35 (2.3)	0
Eye redness	13 (1.7)	43 (2.8)	2 (0.7)
Headache	12 (1.6)	20 (1.3)	2 (0.7)
Instillation site burning	6 (0.8)	51 (3.4)	2 (0.7)
Instillation site stinging	6 (0.8)	30 (2.0)	2 (0.7)
Nasopharyngitis	18 (2.4)	42 (2.8)	2 (0.7)
Pharyngolaryngeal pain	14 (1.9)	12 (0.8)	6 (2.1)
Group 2	N = 277	N =271	
Eye irritation	1 (0.4)	3 (1.1)	
Eye redness	0	3 (1.1)	
Headache	2 (0.7)	4 (1.5)	
Influenza	1 (0.4)	3 (1.1)	
Nasopharyngitis	2 (0.7)	4 (1.5)	

Note: Incidence is calculated based on number of eyes experiencing a treatment-emergent adverse event.
Percentages are calculated using the number of eyes in each treatment and group.
Group 1 includes trials 05-003-10 and 06-003-09 and Group 2 includes trials 05-003-11, 05-003-13 and 09-003-05.
[a] Treatment-emergent adverse events are defined as those events that are started on or after study medication instillation.
[b] MedDRA dictionary (version 7.0) is used for coding.
[c] An eye is counted only once even if it had more than one occurrence of adverse event in a preferred term class.

In Group 1 (Protocols 05=003-10 and 06-003-09), no TEAE occurred in >4% of eyes in any treatment group. Ocular TEAEs to occur in ≥1% of alcaftadine-treated eyes in Group 1 were eye irritation, eye pruritus, eye redness, instillation site burning and instillation site stinging. Non-ocular TEAEs to occur in ≥1% of alcaftadine-treated eyes in Group 1 were headache and nasopharyngitis. With the exception of headache and pharyngolaryngeal pain, all TEAEs in this table were more common in alcaftadine-treated eyes in Group 1 than in Vehicle (placebo)-treated eyes. It should be noted, however, that there was a marked difference in the sample size of the three treatment groups (1512 alcaftadine-treated eyes, 744 Vehicle-treated eyes and 292 Patanol-treated eyes).

In Group 2 (Protocols 05-003-11, 05-003-13 and 09-003-05), no TEAE occurred in >1.5% of eyes in either treatment group. The only ocular TEAEs to occur in ≥1% of alcaftadine-treated eyes in Group 2

were eye irritation and eye redness. Non-ocular TEAEs to occur in ≥1% of Alcaftadine-treated eyes in Group 2 were headache, influenza and nasopharyngitis. The incidence of all of these TEAEs was higher in alcaftadine-treated eyes in Group 2 than in Vehicle (placebo)-treated eyes. In this case, the sample size of both treatment-groups was similar, and both treatments were administered in all three studies in this group.

Safety Summary Statement

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.

The most common ocular adverse reactions, occurring in < 4% of alcaftadine ophthalmic solution 0.25% -treated eyes, were eye irritation, burning and/or stinging on instillation, eye redness, and eye pruritus.

9. Advisory Committee Meeting

Although the drug substance alcaftadine is a new molecular entity, the adverse events observed with the use of this product are consistent with the events known to be observed for this class of drugs (topical H_1 antagonists). FDA Advisory Committee meetings have been held in the past for drug products in this class. The Committee has agreed with the approach taken for the development and evaluation of these products.

There was concurrence between the Division of Anti-Infective and Ophthalmology Products and the Office of Anti-Microbial Products that this drug product, alcaftadine ophthalmic solution 0.25%, did not present any new or problematic chemistry/manufacturing issues, preclinical issues, or clinical issues to warrant convening an FDA Advisory Committee Meeting. There was concurrence that no FDA Advisory Committee Meeting need be convened for alcaftadine ophthalmic solution 0.25%.

10. Pediatrics

This drug was tested in a pediatric population. Safety and efficacy of alcaftadine ophthalmic solution 0.25% have not been established in pediatric patients less than 2 years of age because the diagnosis of allergic conjunctivitis cannot be reliably made in patients of this age. Efficacy in pediatric patients under 10 years of age was extrapolated from clinical trials conducted in patients greater than 10 years of age because there are no differences in the clinical characteristics or course of the disease at any age.

11. Other Relevant Regulatory Issues

DSI

A Division of Scientific Investigations (DSI) audit was requested. Per the DSI review finalized 6/9/2010: Two protocols were inspected to assess data integrity and human subject protection (09-003-05 and 05-003-11).

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.

FINANCIAL DISCLOSURE

The applicant has examined its financial data regarding significant payments of other sorts made to all investigators in the studies and equity information as provided by the investigators, as defined in 21 CFR 54.2. There is no evidence to suggest that the results of the study were impacted by any financial payments.

DMEPA

The Division of Medication Errors and Technical Support (DMETS) originally reviewed (b) (4) as the proposed proprietary name for alcaftadine ophthalmic solution in response to a DAIOP consult in September 2006 under IND 66,884. There was no objection to the use of the proprietary name, (b) (4). This was considered a tentative decision, and this name with its associated labels and labeling were to be reevaluated upon submission of the NDA and approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to approval was expected rule out any objections based upon approvals of other proprietary or established names from the signature date of this document.

The Division of Medication Error Prevention and Analysis (DMEPA) Proprietary Name Risk Assessment evaluated (b) (4) as the proposed proprietary name for alcaftadine ophthalmic solution. This proposed name was evaluated from a safety and promotional perspective based on the product characteristics provided by the Applicant. DMEPA sought input from pertinent disciplines involved with the review of this application. While there is a difference of opinion with the clinical review team in the potential risk, DMEPA's evaluation concluded that the proposed name, (b) (4), was vulnerable to name confusion with the marketed proprietary name, Xalatan, because of the orthographic similarities and overlapping product characteristics shared by this name pair. Thus, DMEPA objected to the use of the proposed proprietary name, (b) (4), for the product.

On May 10, 2010, the applicant submitted a request for review of a different proprietary name, (b) (4) This name was withdrawn by the applicant in July 7, 2010, based on feedback from DMEPA that the name was too similar to "Mylanta."

In this July 7, 2010, submission the applicant proposed (b) (4) as a new primary proprietary name and "Lastacaft" as an alternate proprietary name. (b) (4) was withdrawn by the applicant based on feedback from DMEPA that the name was too similar to "Nevanac"; Lastacaft was found acceptable

by DMEPA as conveyed in a teleconference with the applicant on July 19, 2010. The applicant will formally submit Lastacaft as the new primary proprietary name.

DMEPA also provided recommendations on the packaging configuration and the package insert labeling. Specifically, their recommendation:

> 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.

was not utilized. The American Academy of Ophthalmology (AAO) recommendations for cap color corresponding to drug class are not meant to preclude the use of colors on the carton or container labeling. The appropriate cap color for topical products in this class is white, as is reflected in the alcaftadine packaging.

DDMAC

The Division of Drug Marketing, Advertising, and Communications (DDMAC) reviewed the proposed product labeling, including the package insert (PI), draft carton label, and draft container label for (b) (4) (alcaftadine ophthalmic solution) 0.25%, dated 5/7/2010. See italics for recommendations.

Regarding the Highlights Section:

> *Comment [np1]: We note that the Warnings and Precautions section is not included as part of the Highlights of Prescribing Information section, but is included in for Bepreve (a product with a similar indication and similar Warnings and Precautions). Please consider adding relevant information from the Warnings and Precautions section of the Full Prescribing Information.*
>
> *Comment [np2]: Should this cross reference be changed from 2.1 to 2? Currently, 2.1 is not a section within the (b) (4) PI.*
>
> *Comment [np3]: This date needs to be updated.*

Warnings and Precautions are part of the final label. Dosage and Administration cross references Section 2 in the final label. Revision date for final label is updated.

Regarding the Table of Contents Section:

> *Comment [np4]: Should this be deleted to ensure consistency with the (b) (4) Full Prescribing Information? Currently, 2.1 is not a section within the (b) (4) PI.*

There is no Section 2.1 in the final label.

Regarding the Dosage and Administration Section:

> *Comment [np5]: In accordance with the March 2010 Guidance for Industry: Dosage and Administration Section of Labeling for Human Prescription Drug and Biological Products - Content and Format, please include the following: Route of administration when there is a potential for confusion and serious safety consequences if administered by the wrong route (e.g., For Topical Use Only or For Intravenous Use Only). . . . There should be cross-referencing to any section in labeling that contains more detailed discussions of the critical information or recommendations placed at the beginning of the DOSAGE AND ADMINISTRATION section. Please consider adding a cross reference to section 5.3*
>
> *Comment [np6]: We note that Elestat, which has the same indication and similar MOA, contains the following statement "Treatment should be continued throughout the period of exposure (i.e., until the pollen season is over or until exposure to the offending allergen is terminated), even when symptoms are absent" in the Dosage and Administration section of the Elestat PI. Should a similar statement be included in this section to provide direction regarding the duration of therapy? Is there a maximum time that* (b) (4) *should be used?*

The final labeling in this Section is consistent with the Bepreve labeling. Drops cannot be administered to the eye intravenously or orally, and there are no serious safety consequences anticipated.

Modeling the alcaftadine label strictly by the Elestat label is not appropriate. The Elestat label has not been updated in the new PLR format.

Regarding the Warnings and Precautions Section:

> *Comment [np7]: Please add the Trademark symbol anytime the brand name* (b) (4) *is used in this PI.*

The Agency is not responsible for placing the Trademark symbol within labeling; that responsibility falls on the applicant if they wish to denote a Trademark name.

Regarding the Adverse Events Section:

> *Comment [np8]: In accordance with the January 2006 Guidance for Industry: Adverse Reactions Section of the Label for Human Prescription Drugs and Biologics – Content and Format, please include the following: Please include an adequate description of the data sources for the adverse event data, as outlined in the guidance. For example, please include information on whether the trials were double blinded, randomized, and placebo controlled trials, if available. Also, please include the dosage, frequency, and duration of therapy that patients received. Identify adverse reactions, if any that resulted in a significant rate of discontinuation or other clinical intervention (e.g., dosage adjustment, need for other therapy to treat an adverse reaction) in clinical trials. Additionally, please identify the specific rates for the most frequently reported adverse reactions in the* (b) (4) *study/studies listed in this section.*

Comment [np9]: We note that a similar statement is within the Elestat PI, however this statement could still potentially be used to make claims in promotion regarding the guaranteed safety of this product. Please delete this statement and consider including only specific adverse reactions which were proven to be caused by the drug, if that information is available.

The final labeling in this Section is consistent with the Bepreve labeling.

The addition of these statements to the Adverse Events Section is not recommended. The adverse events noted in Section 6 of the labeling were seen in all phases of development, including the conjunctival allergen challenge studies and the six week safety study. There were no adverse reactions resulting in a significant rate of discontinuation.

The statement, "Some of these events were similar to the underlying disease being studied," is retained in this Section. This statement does not guarantee the safety of this product; it describes the nature of the disease being treated and the limitations of trial design for allergic conjunctivitis.

Regarding the Clinical Pharmacology Section:

Comment [np10]: Should this statement be revised to state that (b) (4) *is an inhibitor of the release of histamine from mast cells similar to the Bepreve PI?*

The final labeling for this section makes reference to mast cell inhibition.

Regarding the Clinical Trials Section:

Comment [np11]: Please consider including the number of patients that were evaluated in the CAC studies and a description of the study design for these CAC studies along with the dosage, frequency, duration of treatment.

Comment [np12]: Please consider deleting the term (b) (4) *Please include quantifying measures of the outcomes of the clinical study.*

The addition of these statements to the Clinical Trials Section is not recommended. The trials failed on one of their primary endpoints, ocular redness. The efficacy information provided on itching was obtained from the conjunctival antigen challenge model using a placebo control. Supplying statistics for itching in tabular format would likely overstate the efficacy of the drug in promotional materials.

The word (b) (4) is not (b) (4) it describes the endpoints utilized in allergic conjunctivitis trials.

BIOSTATISTICS
Per the Biostatistics consultative review finalized 5/7/2010:

The efficacy of alcaftadine in preventing itching associated with allergic conjunctivitis was supported by three efficacy studies using the conjunctival allergen challenge (CAC) model. In these Phase 3 CAC studies, treatment with alcaftadine led to approximately one unit or greater than one unit improvement in the ocular itching score for alcaftadine-treated eyes compared with vehicle-treated eyes at all post-allergen challenge time points at Visits 3 and 4. These improvements are clinically meaningful, as well as statistically significant ($p<0.001$).

The clinical development program for alcaftadine had intended to demonstrate superiority of alcaftadine to vehicle for both ocular itching and conjunctival redness. However, alcaftadine was unable to demonstrate clinical significance compared to vehicle in preventing conjunctival redness. Therefore, alcaftadine is recommended only for the approval for the prevention of the itching associated with allergic conjunctivitis.

12. Labeling

NDA 22-134, Lastacaft (alcaftadine ophthalmic solution) 0.25% is recommended for approval for the prevention of itching associated with allergic conjunctivitis with the labeling found in the Appendix at the end of this CDTL review (submitted by Vistakon Pharmaceuticals, Inc. on 7/21/2010 and 7/22/2010).

13. Recommendations/Risk Benefit Assessment

RECOMMENDED REGULATORY ACTION:
NDA 22-134, Lastacaft (alcaftadine ophthalmic solution) 0.25% is recommended for approval for the prevention of itching associated with allergic conjunctivitis. There is substantial evidence of safety and effectiveness consisting of adequate and well controlled studies which demonstrate that patients receiving Lastacaft (alcaftadine ophthalmic solution) 0.25% experienced a statistically and clinically significant response in the reduction of ocular itching. The data support Lastacaft (alcaftadine ophthalmic solution) 0.25% administered once a day for the prevention of itching associated with allergic conjunctivitis.

RISK BENEFIT ASSESSMENT:
The results from the three efficacy trials (Protocols 05-003-11, 09-003-5, and 05-003-13), demonstrates a statistically significant and clinically relevant difference between alcaftadine ophthalmic solution and vehicle for the prevention of ocular itching associated with allergic conjunctivitis.

The most frequent ocular adverse reactions, occurring in < 4% of alcaftadine-treated eyes, were eye irritation, instillation site burning, eye redness, eye pruritus, and instillation site stinging. The most

frequent non-ocular adverse reactions, occurring in < 3% of subjects with alcaftadine-treated eyes, were nasopharyngitis, headache and influenza. Some of these events were similar to the underlying disease being studied.

The benefits of using this drug product outweigh the risks for the above indication.

Pharmacology/Toxicology, CMC, Biostatistics, Clinical, Clinical Pharmacology, and Product Quality Microbiology have recommended approval for this application.

RECOMMENDATION FOR POSTMARKETING RISK MANAGEMENT ACTIVITIES:
There are no risk management activities recommended beyond the routine monitoring and reporting of all adverse events.

There are no recommended Postmarketing Requirements or Phase 4 Commitments.

7 pp of Draft labeling withheld in full immediately following this page as (b)(4).

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22134	ORIG-1	VISTAKON PHARMACEUTICALS LLC	ALCAFTADINE OPHTHALMIC SOLUTION O.25%

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

/s/

WILLIAM M BOYD
07/23/2010

WILEY A CHAMBERS
07/23/2010