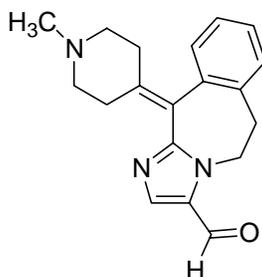


Division Director Review for NDA 22-134

Date	July 23, 2010
From	Wiley A. Chambers, M.D.
NDA #	22-134
Applicant	Vistakon Pharmaceuticals, LLC
Date of Submission	September 29, 2009
Type of Application	505(b)(1)
Name	Lastacft (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)-5H-imidazo[2,1-b] [3] benzazepine-3-carboxaldehyde

Lastacft (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 Lastacft (alcaftadine ophthalmic solution) 0.25% as the proposed active ingredient has not been previously approved in the United States or abroad.

2. Background

The efficacy endpoints chosen for the phase 3 studies have been widely used in clinical studies of ophthalmic solutions for the evaluation of the efficacy and safety of investigational products for allergic conjunctivitis. For an indication for the treatment of allergic conjunctivitis, a demonstration of efficacy is recommended 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 exposure 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

A summary of the clinical studies 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 05-003-11, 05-003-13 and 09-003-05 were efficacy trials using the CAC (Conjunctival Antigen Challenge) study model. They included subjects > 10 year in age because it was agreed that subjects less than 10 years old could not reliably describe the subjective endpoint of itching. These trials were successful for itching but failed for ocular redness.

After having performed 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

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 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. 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 (b) (4) (LDPE) bottle, dropper tip, and a (b) (4) 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)	(b) (4)
Edetate Disodium, Dihydrate	(b) (4)	(b) (4)
Sodium Chloride	(b) (4)	(b) (4)
Benzalkonium Chloride	(b) (4)	(b) (4)
NaCl and/or HCl	pH adjustment to 7.0 target	pH adjustment
Purified Water	(b) (4)	(b) (4)

Proposed Regulatory Specifications:

(b) (4)

4. Nonclinical Pharmacology/Toxicology

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.

In a 6-month oral repeated-dose study in rats, slight to moderate toxicity occurred at R89674 doses of ≥ 20 mg/kg/day. The NOAEL for this study was considered to be 5 mg/kg/day and R90692 AUC_{0-t} values associated with this dose were 0.627 (male) and 0.493 (female) $\mu\text{g} \times \text{h/mL}$.

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 AUC_{0-∞} value of 29.6 $\mu\text{g} \times \text{h/mL}$.

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 abnormalities of the liver in rat, the exposure levels associated with the higher doses. 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-last} of 10.613 ng \times h/mL in the clinical pharmacokinetic protocol # 05-003-09.

5. Clinical Pharmacology/Biopharmaceutics

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. 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

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 (b) (4) at (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. 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)

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

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)	Protocol 09-003-05 (Vehicle N=30 ^c) (Alcaftadine N=30 ^c)	Protocol 05-003-13 (Vehicle N=87 ^b) (Alcaftadine N=89 ^b)
	Difference^d p-Value^e	Difference^d p-Value^e	Difference^d p-Value^e
Visit 3 (16 hours post dose)			
3 Min. Post-Challenge	-0.87 (p<0.001)	-1.73 (p<0.001)	-1.09 (p<0.001)
5 Min. Post-Challenge	-0.96 (p<0.001)	-1.69 (p<0.001)	-1.22 (p<0.001)
7 Min. Post-Challenge	-0.96 (p<0.001)	-1.58 (p<0.001)	-1.11 (p<0.001)
Visit 4 (15 min post dose)			
3 Min. Post-Challenge	-1.34 (p<0.001)	-1.50 (p<0.001)	-1.32 (p<0.001)
5 Min. Post-Challenge	-1.32 (p<0.001)	-1.49 (p<0.001)	-1.26 (p<0.001)
7 Min. Post-Challenge	-1.24 (p<0.001)	-1.47 (p<0.001)	-1.17 (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 -0.87 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 the majority of 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)	Protocol 09-003-05 (Vehicle N=30 ^c) (Alcaftadine N=30 ^c)	Protocol 05-003-13 (Vehicle N=87 ^b) (Alcaftadine N=89 ^b)
	Difference^d p-Value^e	Difference^d p-Value^e	Difference^d p-Value^e
Visit 3 (16 hours post dose)			
7 Min. Post-Challenge	-0.41 (p<0.001)	-0.95 (p<0.001)	-0.37 (p=0.006)
15 Min. Post-Challenge	-0.40 (p =0.002)	-0.54 (p=0.009)	-0.24 (p=0.054)
20 Min. Post-Challenge	-0.37 (p=0.003)	-0.54 (p=0.005)	-0.18 (p=0.131)
Visit 4 (15 min. post dose)			
7 Min. Post-Challenge	-0.80 (p<0.001)	-0.88 (p<0.001)	-0.53 (p<0.001)
15 Min. Post-Challenge	-0.70 (p<0.001)	-0.61 (p=0.007)	-0.14 (p=0.173)
20 Min. Post-Challenge	-0.58 (p<0.001)	-0.58 (p=0.011)	-0.09 (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 one (1) unit at the majority of time points 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. There is **not** substantial evidence that patients receiving alcaftadine ophthalmic solution 0.25% experienced a clinically significant response in the reduction of ocular redness.

8. Safety

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.

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 – Single drop exposure			
05-003-11	N=42 (1 eye) N=40 (2 eyes)	N=44 (2 eyes)	
05-003-13	N=29 (1 eye) N=30 (2 eyes)	N=29 (2 eyes)	
09-003-05 (Modified Formulation of alcaftadine)	N=30 (2 eyes)	N=30 (2 eyes)	

^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%.

Adverse Events

Incidence \geq 1 % Treatment-Emergent Adverse Events (TEAE) by Preferred Term and Treatment (Safety Population)

Preferred Term	Vehicle n (%)	Alcaftadine n (%)	Patanol [®] n (%)
6 week studies	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)

Note: Incidence is calculated based on number of eyes experiencing a treatment-emergent adverse event. An eye is counted only once even if it had more than one occurrence of adverse event in a preferred term class. 6 week studies include trials 05-003-10 and 06-003-09. Trials 05-003-11, 05-003-13 and 09-003-05 due to their study design are not adequate for safety evaluations. Treatment-emergent adverse events are defined as those events that are started on or after study medication instillation.

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 H₁ 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, 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 [REDACTED] (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, [REDACTED] (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 [REDACTED] (b) (4) as the proposed proprietary name. 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 "Lastacraft" 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"; Lastacraft was found acceptable by DMEPA as conveyed in a teleconference with the applicant on July 19, 2010. The applicant formally submitted Lastacraft as the new primary proprietary name.

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 Lastacraft (alcaftadine ophthalmic solution) 0.25%, dated 5/7/2010. Comments have been considered as discussed in the Cross Discipline Team Leader Review.

BIostatISTICS

The Biostatistical review concurred that the efficacy of alcaftadine in preventing itching associated with allergic conjunctivitis was supported by three efficacy studies using the conjunctival allergen challenge (CAC) model. The improvement in itching was considered clinically meaningful, as well as statistically significant ($p < 0.001$). While the clinical development program for alcaftadine had intended to demonstrate superiority of alcaftadine to vehicle for both ocular itching and conjunctival redness, alcaftadine was unable to demonstrate clinical significance compared to vehicle in preventing conjunctival redness. Therefore, alcaftadine was recommended only for the approval for the prevention of the itching associated with allergic conjunctivitis.

12. Labeling

NDA 22-134, Lastacraft (alcaftadine ophthalmic solution) 0.25% is recommended for approval for the prevention of itching associated with allergic conjunctivitis with the following labeling.

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use LASTACAFT™ safely and effectively. See full prescribing information for LASTACAFT™.

LASTACAFT™ (alcaftadine ophthalmic solution)
Initial U.S. Approval: 2010

----- INDICATIONS AND USAGE-----

LASTACAFT™ is a H₁ histamine receptor antagonist indicated for the prevention of itching associated with allergic conjunctivitis (1)

-----DOSAGE AND ADMINISTRATION-----

Instill one drop in each eye once daily. (2)

-----DOSAGE FORMS AND STRENGTHS-----

Ophthalmic solution containing alcaftadine, 0.25% (2.5 mg/mL) (3)

-----WARNINGS AND PRECAUTIONS-----

- To minimize the risk of contamination, do not touch dropper tip to any surface. Keep bottle tightly closed when not in use. (5.1)

- LASTACAFT™ should not be used to treat contact lens-related irritation. (5.2)
- Remove contact lenses prior to instillation of LASTACAFT™. (5.2)

-----ADVERSE REACTIONS-----

The most common ocular adverse reactions, occurring in < 4% of LASTACAFT™-treated eyes, were eye irritation, burning and/or stinging on instillation, eye redness, and eye pruritus. (6.1)

The most common non-ocular adverse reactions, occurring in < 3% of subjects with LASTACAFT™-treated eyes, were nasopharyngitis, headache and influenza (6.2)

To report SUSPECTED ADVERSE REACTIONS, contact Vistakon Pharmaceuticals, LLC at 1-800-523-6225 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for Patient Counseling Information

Revised: 05/2010

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

LASTACAFT™ is a H₁ histamine receptor antagonist indicated for the prevention of itching associated with allergic conjunctivitis.

2 DOSAGE AND ADMINISTRATION

Instill one drop in each eye once daily.

3 DOSAGE FORMS AND STRENGTHS

Topical ophthalmic solution containing alcaftadine, 0.25% (2.5 mg/mL).

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Contamination of Tip and Solution

To minimize contaminating the dropper tip and solution, care should be taken not to touch the eyelids or surrounding areas with the dropper tip of the bottle. Keep bottle tightly closed when not in use.

5.2 Contact Lens Use

Patients should be advised not to wear a contact lens if their eye is red.

LASTACAFT™ should not be used to treat contact lens-related irritation.

LASTACAFT™ should not be instilled while wearing contact lenses. Remove contact lenses prior to instillation of LASTACAFT™. The preservative in LASTACAFT™, benzalkonium chloride, may be absorbed by soft contact lenses. Lenses may be reinserted after 10 minutes following administration of LASTACAFT™.

5.3 Topical Ophthalmic Use Only

LASTACAFT™ is for topical ophthalmic use only.

6 ADVERSE REACTIONS

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

6.1 Ocular Adverse Reactions

The most frequent ocular adverse reactions, occurring in < 4% of LASTACAFT™-treated eyes, were eye irritation, burning and/or stinging upon instillation, eye redness and eye pruritus.

6.2 Non-ocular Adverse Reactions

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B. Reproduction studies performed in rats and rabbits revealed no evidence of impaired female reproduction or harm to the fetus due to alcaftadine. Oral doses in rats and rabbits of 20 and 80 mg/kg/day, respectively, produced plasma exposure levels approximately 200 and 9000 times the plasma exposure at the recommended human ocular dose. There are however, no adequate and well controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

8.3 Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are

excreted in human milk, caution should be exercised when LASTACFT™ is administered to a nursing woman.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients below the age of 2 years have not been established.

8.5 Geriatric Use

No overall differences in safety or effectiveness were observed between elderly and younger subjects.

11 DESCRIPTION

LASTACFT™ is a sterile, topically administered H₁ receptor antagonist containing alcaftadine for ophthalmic use.

Alcaftadine is a white to yellow powder with an empirical formula of C₁₉H₂₁N₃O and a molecular weight of 307.39.

Contains:

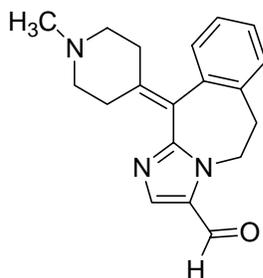
Active: alcaftadine 0.25% (2.5 mg/mL)

Preservative: benzalkonium chloride 0.005%

Inactives: edetate disodium, monobasic sodium phosphate, purified water, sodium chloride, sodium hydroxide and/or hydrochloric acid (to adjust pH)

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

Structural Formula:



The drug product has a pH of approximately 7 and an osmolality of approximately 290 mOsm/kg.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Alcaftadine is a H₁ histamine receptor antagonist and inhibitor of the release of histamine from mast cells. Decreased chemotaxis and inhibition of eosinophil activation has also been demonstrated

12.3 Pharmacokinetics

Absorption

Following bilateral topical ocular administration of alcaftadine ophthalmic solution, 0.25%, the mean plasma C_{max} of alcaftadine was approximately 60 pg/mL and the median T_{max} occurred at 15 minutes. Plasma concentrations of alcaftadine were below the lower limit of quantification (10 pg/mL) by 3 hours after dosing. The mean C_{max} of the active carboxylic acid metabolite was approximately 3 ng/mL and occurred at 1 hour after dosing. Plasma concentrations of the carboxylic acid metabolite were below the lower limit of quantification (100 pg/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.

Distribution

The protein binding of alcaftadine and the active metabolite are 39.2% and 62.7%, respectively.

Metabolism

The metabolism of alcaftadine is mediated by non-CYP450 cytosolic enzymes to the active carboxylic acid metabolite.

Excretion

The elimination half-life of the carboxylic acid metabolite is approximately 2 hours

following topical ocular administration. Based on data following oral administration of alcaftadine, the carboxylic acid metabolite is primarily eliminated unchanged in the urine.

In vitro studies showed that neither alcaftadine nor the carboxylic acid metabolite substantially inhibited reactions catalyzed by major CYP450 enzymes.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Alcaftadine was not mutagenic or genotoxic in the Ames test, the mouse lymphoma assay or the mouse micronucleus assay.

Alcaftadine was found to have no effect on fertility of male and female rats at oral doses up to 20 mg/kg/day (approximately 200 times the plasma exposure at the recommended human ocular dose).

14 CLINICAL STUDIES

Clinical efficacy was evaluated in conjunctival allergen challenge (CAC) studies. LASTACAFT™ was more effective than its vehicle in preventing ocular itching in patients with allergic conjunctivitis induced by an ocular allergen challenge, both at 3 minutes post-dosing and at 16 hours post-dosing of LASTACAFT™.

The safety of LASTACAFT™ was evaluated in a randomized clinical study of 909 subjects over a period of 6 weeks.

16 HOW SUPPLIED/STORAGE AND HANDLING

LASTACAFT™ (alcaftadine ophthalmic solution) 0.25% is supplied in an opaque, white low-density polyethylene bottle with a white polypropylene cap.

3 mL fill in 5 mL bottle (NDC 68669-412-03)

Storage: Store at 15-25°C (59-77°F)

17 PATIENT COUNSELING INFORMATION

17.1 Sterility of Dropper Tip

Patients should be advised to not touch dropper tip to any surface, as this may contaminate the contents.

17.2 Concomitant Use of Contact Lenses

Patients should be advised not to wear a contact lens if their eye is red. Patients should be advised that LASTACAFT™ should not be used to treat contact lens-related irritation. Patients should also be advised to remove contact lenses prior to instillation of LASTACAFT™. The preservative in LASTACAFT™, benzalkonium chloride, may be absorbed by soft contact lenses. Lenses may be reinserted after 10 minutes following administration of LASTACAFT™.

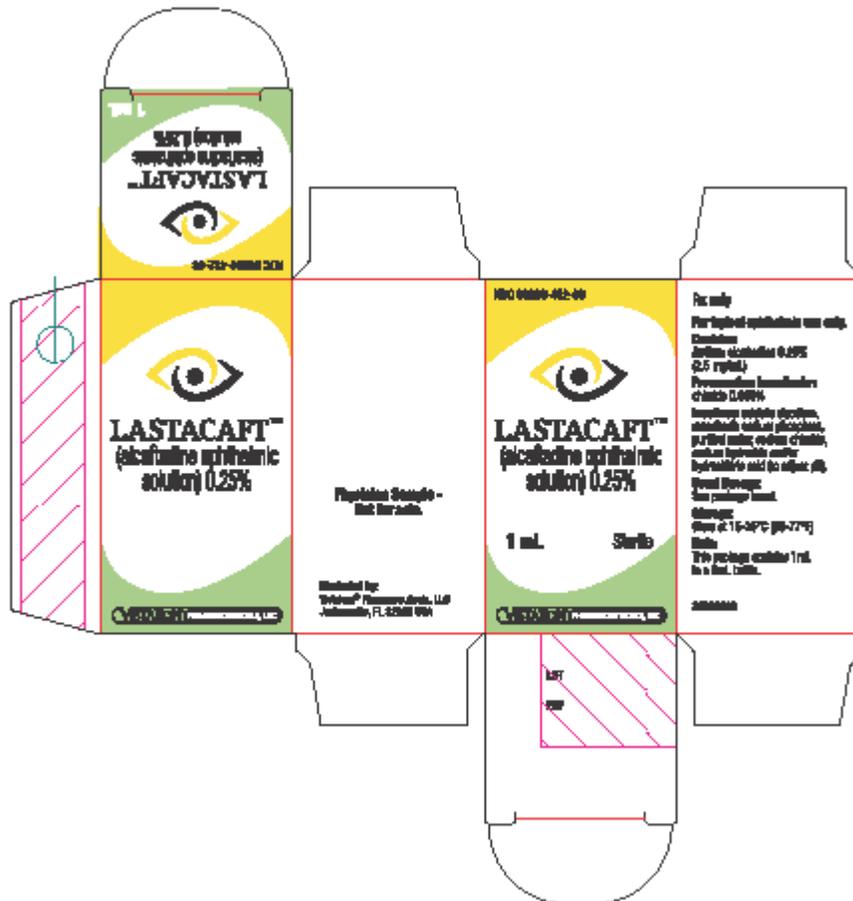
Manufactured for Vistakon Pharmaceuticals, LLC
Jacksonville, FL 32256 USA

Division Director Review
Wiley A. Chambers, M.D.
NDA 22-134
Lastacraft (alcaftadine ophthalmic solution) 0.25%

SAMPLE BOTTLE LABEL 1 MG:



SAMPLE CARTON LABEL 1 MG:



Division Director Review
Wiley A. Chambers, M.D.
NDA 22-134
Lastacraft (alcaftadine ophthalmic solution) 0.25%

COMMERCIAL BOTTLE LABEL 3 MG:



Division Director Review
Wiley A. Chambers, M.D.
NDA 22-134
Lastacast (alcaftadine ophthalmic solution) 0.25%

COMMERCIAL CARTON LABEL 3 MG:



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 as described in the proposed labeling.

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.

Wiley A. Chambers, MD
Acting Director
Division of Anti-Infective and Ophthalmology Products

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22134	ORIG-1	VISTAKON PHARMACEUTICA LS LLC	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/

WILEY A CHAMBERS
07/23/2010