CLINICAL REVIEW

Application Type	NDA
Application Number(s)	22-134
Priority or Standard	S
Submit Date(s)	September 29, 2009
Received Date(s)	September 29, 2009
PDUFA Goal Date	July 28, 2010
Division / Office	DAIOP
Reviewer Name(s)	Martin P. Nevitt, M.D.,M.P.H.
Review Completion Date	April 2, 2010
Established Name	alcaftadine ophthalmic solution, 0.25%
(Proposed) Trade Name	Lastacaft
Therapeutic Class	histamine H_1 receptor antagonist
Applicant	Vistakon Pharmaceuticals, LLC
Formulation(s)	Topical ophthalmic
Dosing Regimen	One drop each eye daily
Indication(s)	Prevention of itching associated with allergic conjunctivitis
Intended Population(s)	Patients ≥ 2 years old

Table of Contents

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

NDA (b) (4) is recommended for approval with the revised labeling identified in this review. The clinical studies contained in this submission support the use of alcaftadine ophthalmic solution 0.25% for the prevention of itching associated with allergic conjunctivitis.

1.2 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 alcatfadine-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.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

There are no proposed risk management actions except the usual post-marketing collection and reporting of adverse experiences associated with the use of drug product.

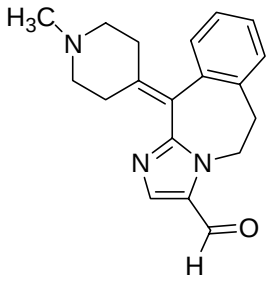
1.4 Recommendations for Postmarket Requirements and Commitments

There are no recommended Phase 4 clinical study commitments.

2 Introduction and Regulatory Background

2.1 Product Information

Chemical Structure of Alcaftadine



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

Alcaftadine is a topically active, direct H1-receptor antagonist and an inhibitor of the release of histamine from mast cells that has been developed for the prevention of itching associated with allergic conjunctivitis.

2.2 Tables of Currently Available Treatments for Proposed Indications

Approved Drugs For Indication of Itching

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

2.3 Availability of Proposed Active Ingredient in the United States

There is no previous marketing experience on Lastacaft (alcaftadine ophthalmic solution) 0.25% as this product is not commercially available.

2.4 Important Safety Issues With Consideration to Related Drugs

Adverse events for this class of drugs (topical H1 antagonists) are well known. Refer to Section 2.2 for currently approved products. 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, phayrngitis, pruritis, rhinitis, sinusitis, sore throat, and taster perversion/bitter taste.

There was adequate AE evaluation for alcaftadine in the submitted trials.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

On November 24, 2003 a Pre-IND meeting was held for the clinical development plan for alcaftadine ophthalmic solution, 0.25% (IND 66,884).

On February 1, 2005 at the End-of-Phase 2 meeting it was agreed that subjects aged 3 and above would be included in a multi-center safety study. While allergic conjunctivitis commonly occurs in pediatric patients above the age of 3 years, it was agreed that pediatric patients less than 10 years of age can not reliably describe the subjective endpoint of itching and that the disease is the same in pediatric patients and adults. Therefore, the efficacy data established in those 10 years and above can be extrapolated down to 3 years of age. A partial waiver for those patients from 0 to 3 years was requested because studies are impossible or highly impractical given the number of pediatric patients 3 years of age or younger with allergic conjunctivitis is so small.

On February 24, 2010 a meeting was held with the Pediatric Research and Equity Act Waivers Committee. The committee concurred with a waiver for studies for the 0 to < 3 year old age group.

2.6 Other Relevant Background Information

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

Formulation	Study #	Study Design	Age	Comments
#PD – F-3730	05-003-10	SAFETY	3+	No serious adverse events / Successful safety study
#PD – F-3730	05-003-11	Efficacy – CAC*	10+	Successful**
#PD – F-3730	05-003-13	Efficacy – CAC*	10+	Successful**
MODIFIED FORMULATION				
#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. (Refer to Section 7.0 Safety for complete results).

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. (Refer to Section 6.0 Efficacy for complete results).

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. (Refer to Section 4.0 for drug formulation). 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.

Reviewer's comments:

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 controlled environment of the conjunctival antigen trial study, 09-003-05 was successful for its efficacy endpoint of ocular itching, though it failed for ocular redness. (Refer to Efficacy Section 6.0)

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

A Division of Scientific Investigations (DSI) audit was requested. Refer to the DSI review for additional information.

3.2 Compliance with Good Clinical Practices

There is no evidence to suggest that the clinical trials were not conducted in compliance with good clinical practices.

3.3 Financial Disclosures

Financial disclosure forms were reviewed. There were no principal investigators with proprietary interest or any significant interest in the drug product in any of the clinical studies.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Ingredient	Formulation #PD-F-3730	Formulation #PD-F-5525-2 (Modified)
	CONCENTRATION (mg/ml)	
Alcaftadine (R89674 – API)	2.5	2.5
(b) (4)		N/A
		N/A
Sodium Phosphate Monobasic Monohydrate, USP	(b) (4)	
Sodium Chloride, USP		
Edetate Disodium Dihydrate, USP		
Benzalkonium Chloride (50% Solution), NF		
Sodium Hydroxide 1N Solution, NF +		
Hydrochloric Acid 1N Solution, NF +		
Purified Water, USP		
(b) (4)		
(b) (4)		

+ as needed for pH adjustment

4.2 Clinical Microbiology

There is no clinical microbiology review for this product. It is not an anti-infective.

4.3 Preclinical Pharmacology/Toxicology

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 doses up to 20 mg/kg/day (1400 times the recommended human ocular dose). (Refer to Pharmacology/Toxicology review for additional preclinical information).

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Alcaftadine is a topically active, direct H1-receptor antagonist and an inhibitor of the release of histamine from mast cells.

4.4.2 Pharmacodynamics

Refer to the Pharmacokinetics section (4.4.3) and the Pharm/Tox review.

4.4.3 Pharmacokinetics

Following bilateral topical ocular administration of alcaftadine ophthalmic solution 0.25%, alcaftadine appears rapidly (median Tmax = 15 min) and briefly in the systemic circulation, falling below quantifiable plasma concentrations of 0.01 ng/mL by 3 hr after dosing. Maximum plasma concentrations achieved were below 0.12 ng/mL. The primary route of elimination of alcaftadine is metabolism to the active carboxylic acid metabolite, which occurs predominately via cytosolic enzymes. The active carboxylic acid metabolite reaches peak plasma concentrations of approximately 3 ng/mL by 1 hr after dosing and plasma concentrations fall near or below the minimum quantification limit (0.10 ng/mL) by 12 hr after dosing. The carboxylic acid metabolite has a dominant t½ of approximately 2 hr and based on data following oral administration, is primarily eliminated unchanged in the urine. There was no indication of accumulation or changes in pharmacokinetics of alcaftadine or the active carboxylic acid metabolite with multiple dosing.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Protocol Number / Formulation	**Primary Objective**	**Study Design/ Population/ Treatment Regimen**	**No. of Subjects Enrolled/ Completed Number of Male/Female Age Range (yr)**
05-003-10 #PD-F-3730	Evaluate the safety of Lastacaft™ 0.25% ophthalmic solution over a 6-week period.	Multicenter, randomized, double-masked, Vehicle (placebo) –controlled, parallel-group safety study. Randomization ratio 2:1 (active:Vehicle). Healthy volunteers ≥3 years of age with normal ocular health. A single drop of Lastacaft™ 0.25% ophthalmic solution or Vehicle in both eyes once daily for 6 weeks.	Enrolled – 909 subjects / Completed – 852 subjects 340/569 3-81 years of age
05-003-11 #PD-F-3730	Establish the efficacy of Lastacaft™ 0.25% 0phthalmic solution compared to Vehicle (placebo) in alleviating the signs and symptoms of CAC induced allergic conjunctivitis at 15 minutes and 16 hours following medication instillation.	Multicenter, randomized, double-masked, Vehicle (placebo)-controlled study using the CAC model. Subjects ≥10 years of age with a history of allergic conjunctivitis or allergic rhinoconjunctivitis. Two single instillations of the assigned study medication 2 weeks apart with a total study duration of approximately 5 weeks. Eligible subjects received Lastacaft™ 0.25% ophthalmic solution bilaterally, Vehicle	Enrolled – 126 subjects / Completed – 123 subjects 43/83 12-78 years of age

		(placebo) bilaterally, or Lastacaft™ 0.25% ophthalmic solution in 1 eye and Vehicle (placebo) in the fellow eye.	
05-003-13 #PD-F-3730	Establish efficacy of Lastacaft™ 0.25% ophthalmic solution compared to Vehicle (placebo) in alleviating the signs and symptoms of CAC induced allergic conjunctivitis at 15 minutes and 16 hours following medication instillation.	Single-center, randomized, double-masked, Vehicle (placebo)-controlled study using the CAC model. Subjects ≥ 10 years of age with a history of allergic conjunctivitis or allergic rhinoconjunctivitis. Two single instillations of the assigned study medication 2 weeks apart with a total study duration of approximately 5 weeks. Eligible subjects received Lastacaft™ 0.25% ophthalmic solution bilaterally, vehicle (placebo) bilaterally, or Lastacaft™ 0.25% ophthalmic solution in 1 eye and Vehicle (placebo) in the fellow eye.	Enrolled – 88 subjects / Completed – 87 subjects 46/42 14-72 years of age
06-003-09 # PD-F-5525*	Evaluate the efficacy, safety, and the affect on quality of life of Lastacaft™ 0.25% ophthalmic solution through an environmental model	Multicenter, randomized, double-masked, vehicle (placebo)- and active (olopatadine)-controlled, parallel group, modified environmental study in adult and pediatric subjects with seasonal allergic conjunctivitis, confirmed by conjunctival allergen challenge (CAC). Vehicle (placebo) ophthalmic solution instilled bilaterally (N=72), Patanol® (olopatadine HCl, 0.1%) instilled bilaterally (N=146), and Lastacaft™ 0.25% ophthalmic solution instilled bilaterally (N=147). Adult and pediatric subjects with a history of seasonal allergic conjunctivitis. Visits on Days 0, 7, 21, and 42.	Enrolled – 365 subjects / Completed – 346 subjects 167/198 10-82 years of age
09-003-05 # PD-F-5525*	Establish the efficacy of Lastacaft™ 0.25% ophthalmic solution compared to Vehicle (placebo) in alleviating the signs and symptoms of CAC induced allergic conjunctivitis at 15 minutes and 16 hours following medication instillation.	Multicenter, randomized, double-masked, Vehicle (placebo)-controlled study using the CAC model. Subjects ≥10 years of age with a history of allergic conjunctivitis or allergic rhinoconjunctivitis. Lastacaft™ 0.25% instilled bilaterally (N=30) Vehicle (placebo) ophthalmic solution instilled bilaterally (N=30)	Enrolled – 60 subjects / Completed – 58 subjects 24/36 11-72 years of age

* Modified Formulation

5.2 Review Strategy

The sources of clinical data utilized in this review include the studies listed in Section 5.1.

5.3 Discussion of Individual Studies/Clinical Trials

The support of clinical efficacy for alcaftadine ophthalmic solution consisted of 3 Conjunctival Antigen Challenge clinical studies (05-003-11, 05-003-13 and 09-003-05). These three CAC studies are two day studies with the subjects instilling the medication once daily on Days 0 and 14 and then being challenged by an ocular antigen. A fourth clinical efficacy study (06-003-09) was a 6 week environmental trial that failed its endpoints but provides data for the safety database.

Reviewer's comments:

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 and avoiding those areas in season where the allergen may be present.

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.

Additional supportive safety data were provided by 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.

Safety Trial

05-003-10: A Multicenter, Randomized, Double-Masked, Vehicle-Controlled, Parallel-Group Study Evaluating the Safety of R89674 (Alcaftadine) 0.25% Ophthalmic Solution Used Once Daily in Healthy, Normal Volunteers

Inclusion Criteria

To be eligible for the trial, subjects must have met all of the following criteria:
1. Males or females of any race at least 3 years of age at Visit 1 (Day 0, baseline).
2. Provided written informed consent and signed HIPAA form. Subjects who were at least 6 years of age and less than 18 years of age must have signed an assent form. In addition, all subjects below the age of 18 years were required to have a parent or legal guardian sign the informed consent.
3. Were willing and able to follow all instructions and attend all study visits.
4. Agreed to and submitted a urine sample for pregnancy testing at Visit 1 and upon exit from the study (if female and of childbearing potential). Childbearing potential was defined as any female who had her first menses, not had a hysterectomy or a bilateral tubal ligation, and had not been postmenopausal for at least 24 months.
5. Ocular health within normal limits, including a calculated best corrected (if necessary) visual acuity of 0.3 logMAR (logarithm of Minimum Angle of Resolution) or better, in each eye as measured using an ETDRS (Early Treatment of Diabetic Retinopathy Study) chart. For subjects under the age of 10 years who were developmentally unable to use the ETDRS chart, a best attempt at visual acuity was made using LEA symbols. For these subjects, 20-foot Snellen equivalent units of 20/63 or better in both eyes was required.

Exclusion Criteria

If subjects met any of the following criteria, they were not to be enrolled in the study:

1. Known contraindications or sensitivities to the use of any of the study medications(s) or their components.
2. History of intraocular surgery and/or have had ocular surgical intervention within 3 months prior to Visit 1 or during the study and/or a history of refractive surgery within the past 6 months.
3. Active ocular disorder with the exception of refractive disorders.
4. Prior (within 5 days of beginning study treatment), current, or anticipated use of any ophthalmic agents other than study medication or contact lenses.
5. Prior (within 2 weeks of beginning study treatment), current, or anticipated use of certain systemic medications, such as corticosteroids, that may have confounded study data or interfered with the subject's study participation.
6. Prior (within 7 days of beginning study treatment) or currently active illness (e.g., upper respiratory tract infection).
7. Prior (within 30 days of beginning study treatment) or anticipated concurrent use of an investigational drug or device.
8. Presence of any condition or situation that, in the investigator's opinion, placed the subject at increased risk, confounded study data, or interfered significantly with the subject's study participation.
9. Planned surgery (ocular or systemic) during the trial period or within 30 days of the study period.
10. Body weight below 5th percentile, for subjects 12 years of age or younger only
11. Currently breastfeeding or planning to breastfeed during the study period.
12.Female less than 18 years of age who was currently pregnant, planning a pregnancy, or had a positive urine pregnancy test at Visit 1.

Exams:

Assessments Performed	Visit 1 (Baseline)	Visit 2	Visit 3	Visit 4
	Day 0	Day 7 +/- 2	Day 21 +/- 3	Day 42 +/- 3
Informed Consent/HIPAA/Assent[a]	X			
Medical & Ophthalmology History	X			
Urine Pregnancy Test[b]	X			X
Body Weight Determination[c]	X			
Physical Exam[d]	X			X
Visual Acuity[e,f]	X	X	X	X
Biomicroscopy[g]	X	X	X	X
Intraocular Pressure[h]	X			X
Ophthalmoscopy[i]	X			X
Instill Study Medication at Office	X	X	X	X
Dispense Study Medication	X	X	X	
Dispense Dosing Diary	X	X	X	
Collection of Returned Study Medication		X	X	X
Collection of Returned Dosing Diary		X	X	X
Assessment of Adverse Events	X	X	X	X
Assessment of Concomitant Medications	X	X	X	X
Exit				X

[a] Assent to be taken from subjects at least 6 years of age and less than 18 years of age.
[b] To be conducted on females of child bearing potential. Child bearing potential is defined as any female who has had her first menses, not had a hysterectomy or bilateral tubal ligation, and has not been post-menopausal for at least 24 months.
[c] For subjects, ≤12 years of age only. The Investigator will refer to Appendix 4.
[d] Physical Exam includes vital signs, body weight, general, head, eyes, ears, nose, throat (HEENT), heart, lungs, abdomen, neurologic, extremities, back, skin, comments
[e] If correction is necessary, best corrected visual acuity will be determined.
[f] For subjects under 10 years of age who are developmentally unable to use ETDRS chart, a best attempt at obtaining visual acuity will be made by using a LEA symbols visual acuity chart (measured as 20-foot Snellen equivalent units).
[g] Evaluated at baseline and 15 minutes post study medication instillation.
[h] Age ≥ 10 years old (if possible)
[i] Dilated, if necessary to observe the posterior pole.

Safety Trial: 05-003-10: Subject Enrollment:

Site	Investigator	Location	Alcaftadine Subjects enrolled	Vehicle Subjects enrolled
1	Ackerman, Stacey, MD	Phil., PA	100	51
2	(b) (4)	Phoenix, AZ	68	33
3	Greiner, Jack, OD,DO, PhD	Andover, MA	201	99
4	Mundorf, Thomas, MD	Charlotte, NC	66	34
5	(b) (4)	Fallston, MD	105	49
6		Las Vegas, NV	69	34
TOTAL			609	300

Primary objective of the Safety Trial and Clinical Endpoints:

The primary objective of Protocol 05-003-10 was to evaluate the safety of alcaftadine ophthalmic solution in healthy, normal subjects. The primary clinical endpoint was to compare adverse events for alcaftadine versus vehicle throughout the study period. The subjects were followed for a period of 6 weeks.

Conjunctival Antigen Challenge (CAC) Efficacy Trials

The three CAC trials (05-003-11, 05-003-13 and 09-003-05) were similar in study design.

05-003-11, 05-003-13 and 09-003-05: Multicenter (or single center), randomized, double-masked, Vehicle (placebo)-controlled study using the CAC model.

Inclusion Criteria

Subjects had to:
1. Be at least 10 years of age of either sex and any race;
2. Provide written informed consent and signed HIPAA form. Subjects who were under the age of 18 needed to sign an assent form as well as having a parent or legal guardian sign an informed consent;
3. Be willing and able to follow all instructions and attend all study visits;
4. If female and of childbearing potential, agree to and submit a urine sample for pregnancy testing at Visit 1 and upon their exit from the study. Child bearing potential was defined as any female who had had her first menses, had not had a hysterectomy or a bilateral tubal ligation, and had not been post menopausal for at least 12 consecutive months;
5. Have a positive history of ocular allergies and a positive skin test reaction to cat hair, cat dander, grasses, ragweed, and/or trees within the past 24 months;
6. Have a calculated best-corrected visual acuity of 0.6 logMAR or better in each eye as measured using an ETDRS chart;
7. Have a positive bilateral CAC reaction (≥ 2 itching and ≥ 2 redness in 2 of the 3 vessel beds) within 10 minutes of instillation of the last titration of allergen at Visit 1;
8. Have a positive bilateral CAC reaction (≥ 2 itching and ≥ 2 redness in 2 of the 3 vessel beds) in at least 2 out of 3 time points at Visit 2;
9. Be able and willing to avoid all disallowed medication for the appropriate washout period and during the study;
10. Avoid wearing contact lenses for at least 3 days prior to and during the study trial period.

Exclusion Criteria

Subjects could not:
1. Have known contraindications or sensitivities to the use of any of the study medications(s) or their components;

2. Have any ocular condition that, in the opinion of the investigator, could affect the subject's safety or trial parameters (particularly narrow angle glaucoma, clinically significant blepharitis, follicular conjunctivitis, iritis, pterygium or a diagnosis of dry eye);
3.Have had ocular surgical intervention within 3 months prior to Visit 1 or during the study and/or a history of refractive surgery within the past 6 months;
4. Have a known history of retinal detachment, diabetic retinopathy, or progressive retinal disease;
5. Have presence of active ocular infection (bacterial, viral or fungal), positive history of an ocular herpetic infection, or preauricular lymphadenopathy at any visit;
6. Manifest signs or symptoms of clinically active allergic conjunctivitis in either eye at the start of Visits 1, 2, 3 or 4 (defined as the presence of any itching or >1 redness in any vessel bed);
7. Use disallowed medications (topical, topical ophthalmic, systemic and/or injectable) during the appropriate pre-study washout period and during the study. Disallowed medications included all anti-allergy therapies including prescription, over the counter or homeopathy, and over the counter sleeping aids. The appropriate pre-study washout period was as follows:
• aspirin, aspirin-containing products or H_1 –antagonist antihistamines (including ocular): 72 hours
• immunotherapeutic agent: treatment must have been maintained steadily for at least 2 months; neither the immunotherapeutic agent nor its dosage could change during the clinical trial
• corticosteroids or mast cell stabilizers (including ocular): 14 days
• all other topical ophthalmic preparations (including tear substitutes) other than the study drops: 72 hours
Note: Currently marketed over the counter anti-allergy eye drops (i.e., anti-histamine/vasoconstrictor combination products Visine-A™ or Naphcon-A®) could be administered to subjects at the end of each visit, after all evaluations were completed.
8. Have any significant illness [i.e., any autoimmune disease, severe cardiovascular disease (including arrhythmias)] the investigator felt could interfere with the subject's safety or study parameters and/or put the subject at any unnecessary risk. This included but was not limited to: poorly controlled hypertension or poorly controlled diabetes, a history of status asthmaticus, a known history of persistent moderate or severe asthma, or a known history of moderate to severe allergic asthmatic reactions to any of the study allergens;
9. Have planned surgery (ocular or systemic) during the trial period or within 30 days after;
10. Have used an investigational drug or device within 30 days of the study, have been previously enrolled in another study using the drug (alcaftadine), or have been concurrently enrolled in another investigational drug or device study;
11. Be a female less than 18 years of age who was pregnant, planning a pregnancy, or had a positive urine pregnancy test at Visit 1.

Exams:

Procedure	**Visit 1 (Day -21+/3)**	**Visit 2 (Day -14+/3)**	**Visit 3 (Day 0)**	**Visit 4 (Day 14+/3)**
IC	**X**			
Demographics	**X**			
History	**X**			
Pregnancy Test(females of childbearing potential)	**X**			**X**
Visual acuity	**X**	**X**	**X**	**X**
Slit lamp	**X**	**X**	**X**	**X**
CAC	**X**	**X**		
Medications		X	X	X
Randomize			X	
Instill study meds			X	X
16 hour post study meds CAC			X	
15 minute post study meds CAC				X
Adverse events		X	X	X
Study exit				X

CAC Trial: 05-003-11: Subject Enrollment

Site	Investigator	Location	Alcaftadine Subjects enrolled	Vehicle Subjects enrolled
1	Ackerman, Stacey, MD	Phil., PA	12	8
2	Lonsdale, John MD	Lewiston, ME	15	8
3	Mundorf, Thomas, MD	Charlotte, NC	24	12
4	Price, Francis, MD	Indianapolis, IN	21	10
5	Schenker, Howard, MD	Rochester, NY	10	6
TOTAL			82	44

CAC Trial: 05-003-13: Subject Enrollment

Site	Investigator	Location	Alcaftadine Subjects enrolled	Vehicle Subjects enrolled
1	(b) (4)		59	29
TOTAL			59	29

CAC Trial: 09-003-05: Subject Enrollment

Site	Investigator	Location	Alcaftadine Subjects enrolled	Vehicle Subjects enrolled
1	Meier, Edward, MD	Mason, OH	15	15
2	Macejko, Thomas, MD	Fairfield, OH	15	15
TOTAL			30	30

Primary objective and Clinical Endpoints of CAC Studies:

The primary objective for the three CAC Studies Protocol 05-003-11, Protocol 05-003-13 and 09-003-05 were to evaluate ocular itching and conjunctival redness.

The primary efficacy variables for the three CAC Studies Protocol 05-003-11, Protocol 05-003-13 and 09-003-05 were:

- Ocular itching evaluated by the subject at 3, 5, and 7 minutes post challenge (0-4 unit scale, allowing half unit increments)
- Conjunctival redness evaluated by the investigator at 7, 15, and 20 minutes post challenge (0-4 unit scale, allowing half unit increments)

Environmental Efficacy and Safety Trial: 06-003-009

The fourth clinical efficacy and safety study was an environmental trial that failed its primary endpoints. The subjects were followed for a period of 6 weeks and are a part of the safety data base included in Section 7 of this review.

06-003-009: A Multicenter, Randomized, Double-masked, Parallel Group Study Evaluating the Efficacy, Safety, and Impact on Quality of Life of Alcaftadine 0.25% Ophthalmic Solution Compared to Vehicle or Olopatadine HCl 0.1% Ophthalmic Solution for 6 Weeks in a Modified Environmental Model in Adult and Pediatric Subjects with Seasonal Allergic Conjunctivitis

Inclusion Criteria

To be enrolled in this study, subjects had to meet the following criteria:
1. Willing and able to read, sign, and date the informed consent and HIPAA documents before undergoing Visit 1 procedures or examinations. Subjects who were under the age of 18 years needed to sign an assent form as well as having a parent or legal guardian sign an informed consent;
2. At least 10 years of age or older and of either sex and any race;
3. Willing and able to make required study visits;
4. Able to follow all study-related instructions;
5. A positive diagnostic test for ragweed within the past 2 years;
6. A positive bilateral ocular response to ragweed as induced by the CAC model at Visit 1;
7. A positive response was defined as itching and redness (in any 1 or more of the following vessel beds: conjunctival, episcleral, ciliary) in both eyes according to the following criteria: scores of $\geq$ 2 for subjects with baseline itching and redness scores of < 1.
OR
An increase of $\geq$ 1 score unit bilateral itching and redness (conjunctival, episcleral, or ciliary) for subjects with baseline itching and redness scores $\geq$ 1.
8. A negative urine pregnancy test if female of childbearing potential (those who were not surgically sterilized [tubal ligation, hysterectomy or bilateral oophorectomy] or post-menopausal [12 months after last menses]) and had to use adequate birth control throughout the study

period. Adequate birth control was defined as hormonal—oral, implantable, injectable, or transdermal contraceptives; mechanical— spermicide in conjunction with a barrier such as condom or diaphragm; intrauterine device; or surgical sterilization of partner;
9. Willing to avoid contact lens wear for each of the study visits, immediately prior to study medication instillation, and for 10 minutes after instillation of study drug. Contact lens wear was to be stable and consistent for 3 months prior to Visit 1.
10.A best corrected logMAR VA score (using the Early Treatment of Diabetic Retinopathy Study [ETDRS] Chart) of 0.60 or better in each eye as measured by ETDRS.

Exclusion Criteria
Subjects could not have met any of the following criteria:
1. A known allergy or sensitivity to any component of the study medication, including preservative(s);
2. Contraindications to the use of the study medication;
3. Pregnant and/or lactating. A negative urine pregnancy test was required for women of childbearing potential at Visit 1 and upon exiting the study;
4. The presence of an ocular infection (bacterial, viral, or fungal) or history of ocular herpes in either eye or presence of preauricular lymphadenopathy;
5. Any ocular condition that, in the investigator's opinion, could have affected the study parameters (particularly, clinically significant blepharitis, follicular conjunctivitis, and iritis);
6. A history of retinal detachment, diabetic retinopathy, or any progressive retinal disease;
7. A history of moderate to severe allergic asthma to any allergen used in this study;
8. A positive diagnosis of dry eye syndrome (i.e., requiring chronic use of artificial tears);
9. A pre-CAC ocular redness score greater than or equal to 3 in either eye;
10. Use of disallowed medications (topical, topical ophthalmic, systemic, and/or injectable) during the appropriate pre-study washout period and during the study. Disallowed medications included all anti-allergy therapies (prescription, over-the-counter [OTC]) and OTC sleeping aids. The appropriate pre-study washout period was as follows:
– H_1–antagonist antihistamines (other than Allegra®, Claritin®, or Zyrtec®, which had a washout period of 7 days): 72 hours
– Immunotherapeutic agent: treatment must have been maintained steadily for at least 2 months; neither the immunotherapeutic agent nor its dosage could change during the clinical trial
– Corticosteroids or mast cell stabilizers (including ocular): 14 days
– All other topical ophthalmic preparations (including tear substitutes) other than the study drops: 72 hours.
Note: Currently marketed OTC anti-allergy eyedrops (i.e., antihistamine/vasoconstrictor combination products like Visine-A™ or Naphcon-A®) could be administered to subjects at the end of each visit, after all evaluations were completed.
11. A recent (within 6 months) clinically relevant history of, or current severe, unstable, or uncontrolled cardiovascular, pulmonary, hepatic, renal, autoimmune disease, and other relevant systemic diseases (e.g., severe chronic obstructive pulmonary disease, cardiac arrhythmia, overt cardiac failure, uncontrolled hypertension, and/or uncontrolled diabetes) that would preclude the safe administration of a topical antihistamine/mast cell stabilizer in the opinion of the

investigator. This included the history of status asthmaticus or a known history of moderate to severe allergic asthmatic reactions to the study allergen used.
12.Participation in another investigational drug or device trial within 30 days of the start of the study or during the study period;
13. Planned surgery during the course of the study;
14. A history or evidence of ocular surgery within 3 months of Visit 1;
15. An employee of the investigator or study center, with direct involvement in the proposed study or other studies under the direction of that investigator or study center, as well as family members of the employees or the investigator.

Exams:

	Visit 1 (Day 0)	Visit 2 (Day 7±3)	Phone Contact (Day 14±3)	Visit 3 (Day 21±3)	Phone Contact (Day 28±3)	Phone Contact (Day 35±3)	Visit 4 (Day 42±3)
IC[a]	X						
Med. History	X	X		X			X
Pregnancy Test[d]	X						
Visual acuity	X	X		X			X
Slit lamp[b]	X	X		X			X
CAC	X						
Symptoms query[c]	X	X	X	X	X	X	X
Randomize	X						
Study meds.	X			X			
Collect diary		X		X			
Adverse events	X	X	X	X	X	X	X
Concomitant meds.	X	X	X	X	X	X	X
Life Questionnaire	X						X
Subject satisfaction							X
Study exit							X

a If washout is required, subjects will sign informed consent prior to washout before Visit 1
b Includes assessment at each study visit of redness, chemosis, cornea, iris and lens by a clinician who is not involved with the dispensing or installation of study medication and from whom the identity of the study medication is concealed
c Subject assessment at each study visit and telephone contact of ocular redness, itching, and tearing three days prior
d Only for women of childbearing potential as defined in the protocol
e Performed at time of early termination if applicable

Environmental Efficacy and Safety Trial: 06-003-009: Subjects Enrolled

	Vehicle	Alcaftadine	Olopatadine	TOTAL
Subjects enrolled	(N = 72)	(N = 147)	(N = 146)	365

Primary objective and Clinical Endpoints of the 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.

Reviewer's comments:

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.

6 Review of Efficacy

Efficacy Summary

6.1 Indication

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

6.1.1 Methods

The support for efficacy for alcaftadine ophthalmic solution comes from three studies: 05-003-11, 05-003-13 and 09-003-05. All three studies used the CAC model of acute conjunctivitis to determine the efficacy of alcaftadine ophthalmic solution, with CAC performed 15 minutes and 16 hours after study medication instillation.

The CAC model is a validated model that creates an allergic response similar to allergic response in an environmental setting. This model is well-accepted as a surrogate of the ocular symptoms of allergic conjunctivitis.

In the two studies 05-003-11 and 05-003-13, subjects were randomly assigned to one of the following treatment arms:

- Alcaftadine ophthalmic solution administered bilaterally
- Alcaftadine ophthalmic solution in one eye and Vehicle (placebo) in the fellow eye (contralaterally)
- Vehicle (placebo) ophthalmic solution administered bilaterally

In the study 09-003-05, subjects were randomly assigned to one of the following treatment arms:

- Alcaftadine ophthalmic solution administered bilaterally
- Vehicle (placebo) ophthalmic solution administered bilaterally

6.1.2 Demographics

Studies 05-003-11 and 05-003-13: (ITT Population)

	Multi-center CAC Study 05-003-13			Single Center CAC Study 05-003-13		
	Vehicle (N=130)[a]	Alcaftadine (N=122)[a]	Total Subjects (%) (N=126)[a]	Vehicle (N=87)[a]	Alcaftadine (N=89)[a]	Total Subjects (%) (N=88)[a]
Age						
≤ 17 years	5	17	11 (8.7)	6	6	6 (6.8)
18-64 years	124	104	114 (90.5)	77	81	79 (89.8)
≥ 65 years	1	1	1 (0.8)	4	2	3 (3.4)
Sex						
Male	44	42	43 (34.1)	36	56	46 (52.3)
Female	86	80	83 (65.9)	51	33	42 (47.7)
Race						
White	113	99	106 (84.1)	82	84	83 (94.3)
Non-White	17	23	20 (15.9)	5	5	5 (5.7)

[a] N represents the number of eyes treated.

Study 09-003-05: (ITT Population)

	Multi-Center Study 09-003-05		
	Vehicle (N=30)[a]	Alcaftadine (N=30)[a]	Total Subjects (N=60)[a]
Age, n (%)			
≤ 17 years	7 (23.3)	2 (6.7)	9 (15.0)
18-64 years	23 (76.7)	27 (90.0)	50 (83.3)
≥ 65 years	0	1 (3.3)	1 (1.7)
Sex, n (%)			
Male	15 (50)	9 (30)	24 (40)
Female	15 (50)	21 (70)	36 (60)
Race, n (%)			
Asian	0	1 (3.3)	1 (1.7)
Non-White	30 (100)	29 (96.7)	59 (98.3)

6.1.3 Subject Disposition

The efficacy results are based on the ITT population for all randomized patients enrolled in the three CAC studies 05-003-11, 05-003-13 and 09-003-05.

Patient Withdrawals from Efficacy Trials

Study	Patient ID#	Treatment	Reason for Discontinuation
05-003-011	50012	Vehicle/Alcaftadine	Took aspirin a disallowed medication
05-003-011	50054	Vehicle/Alcaftadine	Subject choice
05-003-011	50122	Vehicle/Alcaftadine	Subject choice
09-003-05	01016	Alcaftadine	Diagnosed with thyroid goiter
09-003-05	02020	Vehicle	Subject choice
05-003-13	40027	Vehicle	Mild eye pruritus and mild eye redness

6.1.4 Analysis of Primary Endpoint(s)

The primary efficacy variables for CAC Studies Protocol 05-003-11, Protocol 05-003-13 and 09-003-05 were:

- Ocular itching evaluated by the subject at 3, 5, and 7 minutes post challenge (0-4 unit scale, allowing half unit increments)
- 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.
[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.

Reviewer's comments:

To establish efficacy for itching 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 ocular itching 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).

Reviewer's comments:

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 statistically significant difference between alcaftadine ophthalmic solution and vehicle for the prevention of conjunctival redness associated with allergic conjunctivitis.

6.1.5 Analysis of Secondary Endpoints(s)

The secondary efficacy variables for the three CAC studies: 05-003-11, 05-003-13 and 09-003-05 included:

- Ciliary and episcleral redness evaluated by the investigator at 7, 15, and 20 minutes post allergen challenge (0 to 4 scale, allowing half unit increments).
- Chemosis evaluated by the investigator at 7, 15, and 20 minutes post allergen challenge (0 to 4 scale, allowing half unit increments).
- Lid swelling evaluated by the subject at 7, 15, and 20 minutes post allergen challenge (0 to 3 scale).
- Tearing evaluated by the subject at 7, 15, and 20 minutes post allergen challenge (absent or present).
- Ocular mucous discharge evaluated by the investigator at 7, 15, and 20 minutes post allergen challenge (absent or present).
- Rhinorrhea, nasal congestion, nasal pruritus, and ear or palate pruritus evaluated by the subject at 7, 15, and 20 minutes post allergen challenge (absent or present; and severity scale for each item = 0 to 4).
- A nasal symptom composite score of rhinorrhea, nasal congestion, nasal pruritus, and ear or palate pruritus evaluated by the subject at 7, 15, and 20 minutes. The nasal symptom composite score was computed by taking the sum of individual nasal symptoms (rhinorrhea, nasal congestion, nasal pruritus, and ear or palate pruritus) (0 to 16 scale).
- A composite score of presence or absence of at least 1 nasal symptom evaluated by the subject at 7, 15, and 20 minutes (0 to 4 scale).

Reviewer's comments:

Statistically significant reduction was noted for the following secondary efficacy variables of ciliary redness, episcleral redness, chemosis, lid swelling and tearing at some or all post-challenge time points at Visits 3 and 4.

Subjects treated with alcaftadine ophthalmic solution also showed lower incidence and severity of rhinorrhea, nasal congestion, and nasal composite scores at most post-challenge time points at Visits 3 and 4 compared with vehicle (placebo). The nasal pruritus and ear/palate pruritus data were not as consistent because of the lower number of subjects experiencing the symptoms at Visit 2 (Screening).

There were no statistically significant differences noted between alcaftadine ophthalmic solution and vehicle (placebo) for ocular mucous discharge.

6.1.6 Other Endpoints
None.

6.1.7 Subpopulations
Refer to section 6.1.2.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations
In order to demonstrate clinical significance in a CAC study, the difference between groups should be at least one unit on a scale from 0-4 at all the time points evaluated. This endpoint was duplicated in the three CAC trials with the 0.25% concentration of the alcaftadine ophthalmic solution. Therefore, the data supports alcaftadine ophthalmic solution 0.25% at once daily dosing for the prevention of itching associated with allergic conjunctivitis.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects
Long-term effectiveness/tolerance was not evaluated for the clinical efficacy studies. The duration of treatment for the subjects in these trials were single doses at two separate visits [Visit 3 (Day 0; 16 hour post study medication instillation) and Visit 4 (Day 14; 15 minute post study medication instillation)].

6.1.10 Additional Efficacy Issues/Analyses

Study 07-003-10: A comfort study with the Modified Formulation # PD-F-5525
A Single Center, Randomized, Double Masked, Contralateral Comparison of the Relative Safety and Comfort of Alcaftadine 0.25% Ophthalmic Solution as Compared to Tears Naturale® II Placebo) in Adult Subjects with Normal Ocular Health

Criteria for Evaluation:
Comfort Measures: Subjects reported drop comfort ratings on a numeric scale 0 (very comfortable) to 10 (very uncomfortable) immediately after drop instillation and at 30 seconds, 1, 2, 5, and 10 minutes after instillation; drop comfort descriptors (comfortable, cool, refreshing, smooth, soothing, burning, filmy, sticky, irritating, gritty, stinging, and thick) assessed 3 minutes

after drop instillation; and taste perversion ratings (4-point scale) and associated descriptors (bitter, metallic, pleasant, salty, sour, or sweet) assessed at 15 and 30 minutes after drop instillation.

Mean (SD) Comfort Score – Treated Eye[a]

Post-Drop Instillation Time Point	Alcaftadine ophthalmic solution 0.25% (N=30)	Placebo (N=30)	p-Value[b]
Immediate			
Mean (SD)	2.2 (2.23)	1.4 (1.81)	0.065
Median	2.0	1.0	
Range (Min, Max)	(0,8)	(0,7)	
30 Seconds			
Mean (SD)	2.0 (2.10)	0.9 (1.22)	0.003
Median	2.0	0.0	
Range (Min, Max)	(0,8)	(0,4)	
1 Minute			
Mean (SD)	1.8 (1.98)	0.8 (1.19)	0.006
Median	1.5	0.0	
Range (Min, Max)	(0,8)	(0,5)	
2 Minutes			
Mean (SD)	1.4 (1.76)	0.6 (0.86)	0.007
Median	1.0	0.0	
Range (Min, Max)	(0,7)	(0,3)	
5 Minutes			
Mean (SD)	0.9 (1.24)	0.6 (0.86)	0.178
Median	0.5	0.0	
Range (Min, Max)	(0,5)	(0,3)	
10 Minutes			
Mean (SD)	0.5 (1.17)	0.4 (0.77)	0.669
Median	0.0	0.0	
Range (Min, Max)	(0,5)	(0,3)	

[a] Drop comfort assessed on a scale of 0 to 10, where 0=Very Comfortable and 10=Very Uncomfortable
[b] p-Value based on paired t-test comparing treatment difference
SD=standard deviation

Although all subjects rated both treatments as relatively comfortable, the eyes treated with Tears Naturale® II Lubricant Eye Drops (placebo) were consistently scored lower (more comfortable) by subjects as compared to eyes treated with alcaftadine 0.25% ophthalmic solution. Mean comfort scores decreased over time with both alcaftadine 0.25% ophthalmic solution and placebo, however the difference between the alcaftadine 0.25% ophthalmic solution and placebo treatments was statistically significant at 30 seconds (score of 2.0 and 0.9, respectively, p=0.003), 1 minute (score of 1.8 and 0.8, respectively, p=0.006), and 2 minutes (score of 1.4 and 0.6, respectively, p=0.007). By 10 minutes, the mean scores were similar between the eyes treated with alcaftadine 0.25% ophthalmic solution and placebo (0.5 and 0.4, respectively, =0.669).

Reviewer's comments:

With the modified formulation of alcaftadine ophthalmic solution 0.25% subjects rated both drops (alcaftadine 0.25% ophthalmic solution and placebo) at least as comfortable immediately after drop instillation, with scores of 2.2 and 1.4, respectively, and by 10 minutes, the mean scores were similar between the eyes.

7 Review of Safety

Safety Summary

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate 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 in Section 7.3.4.

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 in Section 7.3.4.

Section 5.3 provides additional information of the study design for each of the clinical trials included in the safety data base.

Reviewer's comments:

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

7.1.2 Categorization of Adverse Events

Adverse events were categorized as being mild, moderate to severe. The majority of the adverse events reported were mild to moderate.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

The adverse event data has been pooled for the two 6 week studies (Group 1: Studies 05-003-10 and 06-003-09*)* and pooled data for 2 days of dosing in the CAC studies (Group 2: Studies 05-003-11, 05-003-13 and 09-003-05). Refer to Section 7.3.4.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

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 (94.4)	10 (90.9)	285 (95)	74 (96.1)	472 (92.7)	21 (91.3)	567 (93.1)

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)

Refer to Section 6.1.2 for Demographic information for the three CAC studies (Studies 05-003-11, 05-003-13 and 09-003-05) that provide additional supportive safety information.

Reviewer's comments:

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

7.2.2 Explorations for Dose Response

The only dose of alcafatdine studied in the safety and efficacy clinical trials was 0.25% administered once daily.

7.2.3 Special Animal and/or In Vitro Testing

No special animal or in vitro testing was performed.

7.2.4 Routine Clinical Testing

Following bilateral topical ocular administration of alcaftadine ophthalmic solution 0.25%, alcaftadine appears rapidly (median T_{max} = 15 min) and briefly in the systemic circulation, falling below quantifiable plasma concentrations of 0.01 ng/mL by 3 hr after dosing. Maximum plasma concentrations achieved were below 0.12 ng/mL. The primary route of elimination of alcaftadine is metabolism to the active carboxylic acid metabolite, which occurs predominately via cytosolic enzymes. The active carboxylic acid metabolite reaches peak plasma concentrations of approximately 3 ng/mL by 1 hr after dosing and plasma concentrations fall near or below the minimum quantification limit (0.10 ng/mL) by 12 hr after dosing. The carboxylic acid metabolite has a dominant $t_{½}$ of approximately 2 hr and based on data following oral administration, is primarily eliminated unchanged in the urine. There was no indication of accumulation or changes in pharmacokinetics of alcaftadine or the active carboxylic acid metabolite with multiple dosing.

7.2.5 Metabolic, Clearance, and Interaction Workup

Refer to Section 7.2.4. No clinically noteworthy laboratory abnormalities were detected in any subject during the laboratory evaluation in the pK study.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Adverse events for this class of drugs (topical H1 antagonists) are well known. Refer to Section 2.2 for currently approved products. Common side effects include for 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, phayrngitis, pruritis, rhinitis, sinusitis, sore throat, taste perversion/bitter taste. There was adequate AE evaluation for this product.

7.3 Major Safety Results

7.3.1 Deaths

No deaths were reported in any clinical trial in this development process.

7.3.2 Nonfatal Serious Adverse Events

There were ten subjects that experienced a serious adverse event during the drug development. None of the events were considered to be related to the study medication. Five of the subjects

had received alcaftadine ophthalmic solution 0.25% and experienced the following: 1 – Dyspnea; 1- Premature labor; 1- Drug Abuser; 1- Intervertebral disc protrusion; 1- Gastrointestinal hemorrhage; and 1- Goiter.

In the vehicle group three subjects experienced the following: 1- Asthma; 1-Macular hole and 1-Nephrolithiasis. In the Active control (Patanol) one subject was hospitalized due to a Motor Vehicle Accident.

7.3.3 Dropouts and/or Discontinuations

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 (94.4)	10 (90.9)	285 (95)	74 (96.1)	472 (92.7)	21 (91.3)	567 (93.1)
Discontinued	0	14 (5.6)	1 (9.1)	15 (5.0)	3 (3.9)	37 (7.3)	2 (8.7)	42 (6.9)
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	Hypercholesterolmia, 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 Zooster
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 (92.9)	40 (100)	29 (100)	28 (96.6)	30 (100)	73 (100)	67 (94.4)	70 (100)
Discontinued	0	3 (7.1)	0	0	1 (3.4)	0	0	4 (5.6)	0
Reasons									
Subject Choice	0	2 (4.8)	0	0	0	0	0	2 (2.8)	0
Adverse Event	0	0	0	0	1 (3.4)	0	0	1 (1.4)	0
Other[a]									

[a] Screening failure due to inclusion criteria

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

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 (%)	Total (N=60) n (%)
Randomized	30 (100)	30 (100)	60 (100)
Safety population	30 (100)	30 (100)	60 (100)

Completed	29 (96.7)	29 (96.7)	58 (96.7)
Discontinued	1 (3.3)	1 (3.3)	2 (3.3)
Reasons			
Subject Choice	1 (3.3)	0	1 (1.7)
Adverse Event	0	1 (3.3)	1 (1.7)
Lost to Follow-up	0	0	0

In study 09-003-05 there was only 1 discontinuation due to Adverse Event listed in the table below:

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

Subject Number	Treatment Group	AE Leading to Discontinuation
01016	Alcaftadine	Goiter

7.3.4 Significant Adverse Events
Refer to Section 7.4.1.

7.3.5 Submission Specific Primary Safety Concerns
None.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events
The safety data base includes the two 6 week studies 06-003-09 and 05-003-10; these two studies are Group 1 in the table below.

The three CAC studies 05-003-11, 05-003-13 and 09-003-05, subjects were exposed to the drug for two days, provide additional supportive safety data; these three studies are Group 2 in the table below.

The data from these studies are used to support the product labeling.

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

	Treatment			
Preferred Term[bc]	**Vehicle n (%)**	**Alcaftadine n (%)**	**Patanol® n (%)**	**Total n (%)**
Group 1	N = 744	N = 1512	N = 292	N = 2548
Application site pruritus	0	4 (0.3)	3 (1.0)	7 (0.3)
Eye irritation	16 (2.2)	57 (3.8)	1 (0.3)	74 (2.9)
Eye pruritus	13 (1.7)	35 (2.3)	0	48 (1.9)
Eye redness	13 (1.7)	43 (2.8)	2 (0.7)	58 (2.3)
Headache	12 (1.6)	20 (1.3)	2 (0.7)	34 (1.3)
Instillation site burning	6 (0.8)	51 (3.4)	2 (0.7)	59 (2.3)
Instillation site stinging	6 (0.8)	30 (2.0)	2 (0.7)	38 (1.5)
Nasopharyngitis	18 (2.4)	42 (2.8)	2 (0.7)	62 (2.4)
Pharyngolaryngeal pain	14 (1.9)	12 (0.8)	6 (2.1)	32 (1.3)
Group 2	N = 277	N =271		N = 548
Eye irritation	1 (0.4)	3 (1.1)		4 (0.7)
Eye redness	0	3 (1.1)		3 (0.5)
Headache	2 (0.7)	4 (1.5)		6 (1.1)
Influenza	1 (0.4)	3 (1.1)		4 (0.7)
Nasopharyngitis	2 (0.7)	4 (1.5)		6 (1.1)

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 >3.8% of eyes in any treatment group. Ocular TEAEs to occur in ≥1% of alcaftadine-treated eyes in Group 1 were eye irritation, eye pruritis, 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 application site pruritis and pharyngolaryngeal pain, all TEAEs in this table were more common in alcaftadine -treated eyes in Group 1 than in Patanol®-treated eyes. Similarly, 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). Furthermore, Patanol® was administered in only one of the two studies in this group.

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.

Reviewer's comments:

Alcaftadine ophthalmic solution 0.25% demonstrated an acceptable safety profile.

7.4.2 Laboratory Findings

No clinically noteworthy laboratory abnormalities were detected in any subject during the laboratory evaluation in the pK study.

7.4.3 Vital Signs

Vital signs were also assessed in the study (05-003-09), with no clinically notable changes in any subject noted.

7.4.4 Electrocardiograms (ECGs)

Physical examination findings were assessed in Phase 3 safety study (05-003-10) and in the pK study. No clinically notable changes from baseline were detected in any subject in these studies.

7.4.5 Special Safety Studies/Clinical Trials

Geriatric subjects > 64 years of age were enrolled in the clinical studies throughout the drug's development process. The safety study (05-003-10) enrolled 34 geriatric subjects and the pivotal efficacy studies combined enrolled four subjects. No clinically significant observations in AE profile or ophthalmic assessment data could be made between elderly patients and younger patients across studies.

The safety study (05-003-10) allowed enrollment of pediatric subjects three years of age and older. The three CAC studies (05-003-13, 05-003-11 and 09-003-05) and the environmental study (06-003-09) permitted enrollment of pediatric subjects 10 years of age and older. The other studies in this program did not allow enrollment of subjects younger than 18 years of age. Alcaftadine ophthalmic solution 0.25% was found to be safe and well-tolerated in the pediatric population 3-17 years of age with no unexpected safety issues in any pediatric subject. The type of ocular AEs (mainly eye redness and eye irritation) reported in the pediatric population were generally similar to those reported by the overall population in the study. Only one pediatric subject in the age group 11 to 17 years of age discontinued the study due to a TEAE (urticaria) that was non-ocular in nature and the investigator was doubtful that it was related to study medication. There were no clinically relevant findings on ophthalmic assessment data in the pediatric subjects.

In summary, the safety trial enrolled a total of 114 pediatric subjects of which 77 subjects received alcaftadine ophthalmic solution 0.25%. Of these 77 pediatric subjects, 48 were between 3−10 years of age and 29 were between 11−17 years of age. The three Phase 3 CAC studies, combined, enrolled 23 pediatric subjects 11−17 years of age. Although the number of pediatric subjects studied in this program was relatively small, the safety and efficacy data obtained on this population was no different than the data obtained on adult subjects.

Reviewer's comments:

This data supports the safety of alcaftadine ophthalmic solution 0.25% in the pediatric and geriatric population in the treatment of allergic conjunctivitis.

7.4.6 Immunogenicity
Not applicable.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events
Not observed.

7.5.2 Time Dependency for Adverse Events
There were no time dependent adverse events noted.

7.5.3 Drug-Demographic Interactions
The demographics in the safety population included subjects from age 3 and older. There were no significant differences between alcaftaidine ophthalmic solution 0.25% and the vehicle group with regards to age, gender, ethnicity, eye color or race.

7.5.4 Drug-Disease Interactions
Alcaftadine ophthalmic solution 0.25% was evaluated for the prevention of itching associated with allergic conjunctivitis, and no drug-disease interaction was performed.

7.5.5 Drug-Drug Interactions
No studies were conducted to evaluate a drug-drug interaction between alcaftadine ophthalmic solution 0.25% and any of the concomitant medications allowed in those studies. The low systemic absorption of alcaftadine ophthalmic solution 0.25% would limit the potential for drug interaction.

During the course of the safety studies there were no reports of drug interactions.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Because of the low expected absorption of alcaftadine ophthalmic solution 0.25%, a topical ocular preparation, no carcinogenicity studies were conducted.

The sponsor applied for a waiver for carcinogenicity testing. A waiver for carcinogenicity testing was granted on September 13, 2006.

7.6.2 Human Reproduction and Pregnancy Data

Pregnancy Category B. Reproduction studies have been performed in rats and rabbits at doses of up to 2800 times and 5600 times the human dose respectively, and have revealed no evidence of impaired fertility or harm to the fetus due to alcaftadine. 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.

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 alcaftadine ophthalmic solution 0.25% is administered to a nursing woman.

7.6.3 Pediatrics and Assessment of Effects on Growth

This drug was tested on a pediatric population. Height was not collected as part of this protocol.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There is no anticipated abuse potential for this product. No withdrawal or rebound effects are anticipated.

7.7 Additional Submissions / Safety Issues

On January 28, 2010 the 120 Day Safety Update was filed. No new clinical safety information was included as all the clinical studies were completed at the time of the submission of the original NDA and no clinical studies have been initiated since that time.

8 Postmarket Experience

Alcaftadine ophthalmic solution 0.25% is not marketed in any country.

9 Appendices

9.1 Literature Review References

There is no additional information from the literature.

9.2 Labeling Recommendations

Revised label at the end of this review.

9.3 Advisory Committee Meeting

No Advisory Committee Meeting was held.

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

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/s/

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