

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
21-996

MEDICAL REVIEW(S)



MEMORANDUM

Department Of Health and Human Services
Food and Drugs Administration
Center for Drug Evaluation and Research
Division of Nonprescription Clinical Evaluation

Date: November 10, 2006
From: Andrea Leonard-Segal, M.D.
Director
Subject: NDA 21-996
Alaway
(ketotifen fumarate ophthalmic solution, 0.025%)
Sponsor: Alimera Sciences, Inc.

Background:

Alimera Sciences, Inc proposes to market Alaway, their new ketotifen fumarate ophthalmic solution 0.025%, as an OTC product. The application references the Agency's prior findings of safety and efficacy for NDA 21-066 (Zaditor) to support the safety and efficacy of Alaway. The sponsor conducted one bioequivalence study to demonstrate the bioequivalence of the Alaway formulation to Zaditor.

Ketotifen fumarate ophthalmic solution 0.025% (ZaditorTM) was approved as a prescription product in the United States on July 2, 1999 for the temporary prevention of ocular itching due to allergic conjunctivitis in adults and children ≥ 3 years of age. This product is a relatively selective, noncompetitive histamine antagonist (H1-receptor) and mast cell stabilizer. Zaditor has been shown in clinical studies to be safe and effective for the treatment of ocular itching, but not for ocular redness. There have been millions of patient exposures to Zaditor since it was approved.

Zaditor was switched from prescription to OTC status in October, 2006. (Refer to my October 18, 2006 review.) The indication is: *Temporarily relieves itchy eyes due to pollen, ragweed, grass, animal hair and dander.* The target population is adults and children ≥ 3 years of age. There are other approved topical ophthalmic OTC products for the treatment of ocular itching.

Internal discussions with Dr. Wiley Chambers, Deputy Director of the Division of Anti-Infective and Ophthalmology Products have led to my understanding that for prescription

topical ophthalmologic drugs that treat symptoms of allergic conjunctivitis by blocking histamine effects, the prevention and relief claims are essentially one and the same.

Chemistry:

Refer to the October 27, 2006 review by Dr. Lin Qi. All chemistry issues identified during the review process with this application have been resolved and the reviewer recommends that this NDA can be approved from a chemistry perspective.

Pharmacology/Toxicology:

Refer to the review by Drs. Zhou Chen and Terry Peters. Alaway contains

The pharmacology/toxicology reviewers did not have concerns about the quantity of glycerin in this product from a systemic safety perspective or a local tolerance perspective.

Reproductive studies were reviewed in 1999 under NDA 21-066. Although Zaditor is Pregnancy Category C, the dose at which there is increased incidence of retarded ossification of the sternebrae in laboratory animals is 30,000 times the maximum recommended human ocular dose. Further, clinical studies showed that little systemic exposure to the drug is detected following ocular dosing. The pharmacology/toxicology reviewers consider that the drug exhibits no significant concerns regarding reproductive safety because of the very low systemic exposure to the drug, the previous human experience and the pharmacology/toxicology.

The reviewers conclude that there are no outstanding pharmacology/toxicology issues for ketotifen fumarate, and they recommend "approval" from the pharmacology/toxicology viewpoint.

Microbiology:

Refer to the review by Dr. Bryan S. Riley. He recommends that the product could be approved on the basis of product quality microbiology.

Bioequivalence Study:

Refer to the review by Dr. Lucious Lim.

The sponsor submitted one bioequivalence study comparing Alaway's formulation to that of Zaditor. The study was a single center, prospective, randomized, double-blinded, active and vehicle controlled conjunctival allergen challenge study (CAC). There were 108 subjects (216 eyes) randomized to one of four treatment arms:

- Alaway + Alaway
- Alaway + Vehicle
- Zaditor + Zaditor
- Zaditor + Vehicle

Subjects received one drop of masked study medication in each eye 8 hours prior to CAC at Visit 3 and 15 minutes prior to CAC at Visit 4. The primary efficacy variable was ocular itching for each eye at 3, 5, and 7 minutes following the CAC at Visits 3 and 4.

The mean itching scores of the two treatment arms were comparable. The 95% confidence interval crossed zero at all time points and the mean difference between the mean itching score of the two products was not statistically significant at all time points. Alaway and Zaditor demonstrated equivalence in their ability to decrease ocular itching up to 8 hours post-challenge. Alaway and Zaditor demonstrated equivalence in their ability to decrease ocular itching at 15 minutes post-challenge.

No deaths occurred in the study and there were no serious adverse events related to ketotifen fumarate in the study. The remainder of the safety database provided by the sponsor did not reveal an adverse event profile that would preclude this product from being approved for OTC marketing.

DSI Inspection:

The bioequivalence study (ASI-003) was a single center study and the DSI inspector concluded that the study appeared to have been well conducted.

Pediatrics:

Reference is made to the Agency's finding of safety and efficacy in pediatric patients below the age of 3 years in NDA 21-066. There is safety data for ketotifen fumarate down to about 1 year of age and efficacy has been extrapolated. However, since the Agency has not considered allergic conjunctivitis to reliably exist below the age of 3 years, ketotifen fumarate has been labeled down to age 3 years. It follows that there is no need for additional pediatric studies for this product.

Pregnancy:

The pharmacology/toxicology findings and very low systemic bioavailability of this ocular product do not suggest the need for a pregnancy warning on this product.

Labeling:

There were many labeling issues that arose during the review of this application, but they have all been resolved. Ultimately, the sponsor submitted labeling that is acceptable. Furthermore, the Division of Medication Errors and Technical Support has no objections to the use of the proprietary name "Alaway."

Conclusion:

Alaway is a topical antihistamine/mast cell stabilizer ophthalmologic product indicated for the temporary relief of itchy eyes. This product is bioequivalent to Zaditor, an approved OTC product. There are no scientific, or medical issues to be resolved before this product can be approved.

Recommendation:

Alaway should be approved as an OTC product for the indication: *Temporarily relieves itchy eyes due to pollen, ragweed, grass, animal hair and dander.* The labeling submitted to the Agency by the sponsor is adequate. There is no need for a postmarketing commitment.

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/s/

Andrea Segal
11/29/2006 12:32:20 PM
MEDICAL OFFICER

CLINICAL REVIEW

Application Type NDA 21-996
Submission Number 000
Submission Code Original

Letter Date January 31, 2006
Stamp Date February 1, 2006
PDUFA Goal Date December 1, 2006

Reviewer Name Lucious Lim, M.D., M.P.H.
Review Completion Date September 15, 2006

Established Name Ketotifen fumarate ophthalmic
solution 0.025%
(Proposed) Trade Name Alaway
Therapeutic Class Antihistamine
Applicant Alimera Sciences, Inc.

Priority Designation S

Formulation Active ingredient: ketotifen 0.025%
(equivalent to ketotifen fumarate
0.035%)
Dosing Regimen One drop in the affected eye(s)
twice daily
Indication Temporary relief of itchy eyes due to
ragweed, pollen, grass, animal hair and
dander
Intended Population Adults and children 3 years and older

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**APPEARS THIS WAY
ON ORIGINAL**

1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

It is recommended that NDA 21-996 be approved for over-the-counter use with the labeling revisions listed in this review.

The application supports the safety and effectiveness of ~~—~~ for the temporary relief of itchy eye due to ragweed, pollen, grass, animal hair, and dander.

There are no recommendations for additional postmarketing studies.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

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

1.2.2 Required Phase 4 Commitments

There are no recommended Phase 4 clinical study commitments.

1.2.3 Other Phase 4 Requests

There are no optional or recommended Phase 4 requests.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Ketotifen fumarate ophthalmic solution, 0.025% (Zaditor) is an approved drug product for use by prescription in the United States. Zaditor (NDA 21-066) was approved on July 2, 1999 for the temporary prevention of itching of the eye due to allergic conjunctivitis.

Alaway is an ophthalmic solution containing ketotifen fumarate ophthalmic solution, 0.025% and is indicated for the temporary relief of itchy eye due to ragweed, pollen, grass, animal hair, and dander. The submitted application proposes to market ~~—~~ as an over-the-counter drug product. The application references the Agency's prior findings of safety and efficacy in NDA

21-066 to support the safety and effectiveness of Alaway. Alimera, Inc. conducted a bioequivalence study to demonstrate the bioequivalence of the — formulation to Zaditor.

1.3.2 Efficacy

The application supports the effectiveness of Alaway for the temporary relief of itchy eye due to ragweed, pollen, grass, animal hair, and dander. The application references the Agency's prior findings of efficacy in NDA 21-066 to support the effectiveness of Alaway. The bioequivalence study demonstrates that the Alaway formulation is bioequivalent to Zaditor.

The major sources of clinical data in support of efficacy for — utilized in this review include:

- 1) Agency's findings of efficacy in NDA 21-066
- 2) Study ASI-003 (bioequivalence study comparing Alaway's formulation to Zaditor)

1.3.3 Safety

The application supports the safety of Alaway for the temporary relief of itchy eye due to ragweed, pollen, grass, animal hair, and dander. The application references the Agency's prior findings of safety in NDA 21-066 (Zaditor) to support the safety of Alaway. Zaditor has been marketed in the United States since it was approved on July 2, 1999. Postmarketing experiences data for Zaditor is comparable to the safety data submitted in NDA 21-066.

The major sources of safety data in support of safety for — in this review include:

- 1) Agency's findings of safety in NDA 21-066
- 2) An Alimera-prepared listing of postmarketing experiences compiled from a database generated in July 2005 by the Uppsala Monitoring Center, World Health Organization, Uppsala, Sweden.

1.3.4 Dosing Regimen and Administration

The recommended dose for adults and children 3 years and older is one (1) drop in the affected eye(s) twice daily.

1.3.5 Drug-Drug Interactions

Specific drug interaction studies are not reported. Reference is made to NDA 21-066.

1.3.6 Special Populations

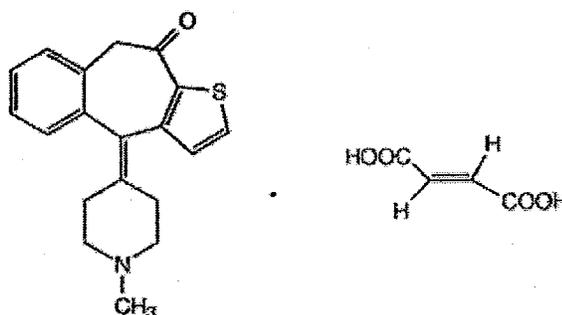
Safety and effectiveness of ketotifen fumarate ophthalmic solution, 0.025% in special populations have been adequately addressed. Reference is made to NDA 21-066.

Safety and effectiveness in pediatric patients below the age of 3 years have not been established.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Alaway (ketotifen fumarate ophthalmic solution, 0.025%) contains 0.345 mg/mL of ketotifen fumarate. It is a sterile ophthalmic solution for use topically to treat ocular itching due to ragweed, pollen, grass, animal hair, and dander. Its chemical name is 4-(1-methylpiperidin-4-ylidene)-4,9-dihydro-10*H*-benzo[4,5]cyclohepta[1,2-*b*]thiophen-10-one hydrogen (*E*)-butenedioate. The active ingredient is represented by the chemical structure:



Ketotifen fumarate is a relatively selective, non-competitive histamine antagonist (H₁-receptor) and mast cell stabilizer. The proposed indication is the temporary relief of itchy eyes due to ragweed, pollen, grass, animal hair, and dander in adults and children 3 years and older. The proposed dosing regimen is one (1) drop in the affected eye(s) twice daily.

2.2 Currently Available Treatment for Indications

There are currently multiple topical antihistamine/decongestant combinations available over-the-counter for relief of allergic conjunctivitis.

2.3 Availability of Proposed Active Ingredient in the United States

There is an approved New Drug Application for ketotifen fumarate [NDA 21-066 for Zaditor (ketotifen fumarate ophthalmic solution, 0.025%) – Novartis] which was approved on July 2, 1999, for prescription only.

2.4 Important Issues With Pharmacologically Related Products

No safety or effectiveness concerns have arisen in other members of this pharmaceutical class, whether marketed or investigational. Reference is made to NDA 21-066.

2.5 Presubmission Regulatory Activity

A Pre-Investigational New Drug Application (PIND 69,164) meeting was conducted on June 25, 2004, to discuss Alimera's planned product development switch from prescriptive to over-the-counter.

A special protocol assessment request was submitted to Pre-IND 69,164 for study ASI-003 (bioequivalence clinical study comparing Alimera's formulation to Zaditor) on December 3, 2004.

Original IND 69,164 was submitted on February 2, 2005. The IND indicated that sponsor intended to develop a new formulation of ketotifen fumarate ophthalmic solution, 0.025% and proposed to demonstrate its equivalence to Zaditor in bioequivalence study ASI-003.

2.6 Other Relevant Background Information

Topical and oral (tablets and elixir) ketotifen fumarate are marketed in the United Kingdom under the trademark Zaditen.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

Drug Product Composition

Component	mg/mL	Function	Quality Standard
Ketotifen Fumarate	0.345	active	Ph. Eur.
Glycerin			
Benzalkonium Chloride			
Sodium Hydroxide			
Hydrochloric Acid			
Water for Injection			

No major CMC issues have been identified to date by the Chemistry Reviewer. The CMC Review has not been finalized.

3.2 Animal Pharmacology/Toxicology

Reference is made to the Agency non-clinical findings in NDA 21-066. No additional animal pharmacology/toxicology studies were performed.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The major sources of clinical data utilized in this review include:

- Agency's findings of safety and efficacy in NDA 21-066
- Bioequivalence study conducted by Alimera (study ASI-003)
- An Alimera-prepared listing of postmarketing experiences compiled from a database generated in July 2005 by the Uppsala Monitoring Center, World Health Organization, Uppsala, Sweden.

4.2 Tables of Clinical Studies

Bioequivalence Study

Study Number and Study Period	Country (No of Study Sites)	Population Studied	Design	Treatment Groups and Dosing Regimen	Study Duration	# Pts Treated	Sex Race
ASI-003 March 10, 2005 to April 15, 2005	USA (1)	Positive ocular allergies ± skin reaction to cat hair, cat dander, grasses, ragweed ± trees and manifests positive allergen challenge at Visits 1 & 2	Single-center, Randomized, double-masked, active- and vehicle-controlled, conjunctival allergen challenge (CAC) study	Alaway OU Zaditor OU Alaway one eye & vehicle fellow eye Zaditor one eye & vehicle fellow eye 1 drop per eye at Visits 3 & 4	5 weeks	n=30 n=30 n=20 n=20	43.5% Male 56.5% Female 91.7% White 5.6% Black 0.9% Asian 1.8% Other

4.3 Review Strategy

The major sources of clinical data utilized in this review include:

- Agency's findings of safety and efficacy in NDA 21-066
- Study ASI-003 (bioequivalence study comparing Alaway's formulation to Zaditor)
- An Alimera-prepared listing of postmarketing experiences compiled from a database generated in July 2005 by the Uppsala Monitoring Center, World Health Organization, Uppsala, Sweden.

4.4 Data Quality and Integrity

A Division of Scientific Investigations (DSI) audit was requested. An audit of the clinical site for Study ASI-003 is ongoing. To date, there is no evidence to suggest that any studies were not conducted in accordance with acceptable clinical ethical standards.

4.5 Compliance with Good Clinical Practices

The applicant's sponsored bioequivalence study was performed in accordance with the principles of good clinical practice.

4.6 Financial Disclosures

The applicant has adequately disclosed financial arrangements with clinical investigators as recommended in the FDA guidance for industry on *Financial Disclosure by Clinical Investigators*.

There is no evidence to suggest that the results of the studies were impacted by any financial payments.

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

Reference is made to the Agency's pharmacokinetic findings in NDA 21-066.

5.2 Pharmacodynamics

Reference is made to the Agency's pharmacodynamic findings in NDA 21-066.

5.3 Exposure-Response Relationships

Adequate assessments of exposure-response relationships were performed in NDA 21-066.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

The proposed indication is:

[]

Reviewer's Comments:

The proposed indication is not acceptable. It is recommended that the indication be changed to read as follows:

For the temporary relief of itchy eyes due to ragweed, pollen, grass, animal hair, and dander,

or

[]

6.1.1 Methods

The major sources of clinical data utilized in this review include:

- Agency's findings of efficacy in NDA 21-066
- Study ASI-003 (bioequivalence study comparing Alaway's formulation to Zaditor)

6.1.2 General Discussion of Endpoints

The proposed primary efficacy endpoint for study ASI-003 (bioequivalence study) was ocular itching post-conjunctival allergen challenge (CAC) at 3, 5, 7 minutes post-CAC at Visit 3 (assessed 8 hours post-dosing) and Visit 4 (assessed 15 minutes post-dosing) which is acceptable.

6.1.3 Study Design

Study ASI-003 was a single-center, prospective, randomized, double-masked, active- and vehicle-controlled, conjunctival allergen challenge (CAC) study designed to show the bioequivalence of Alaway's formulation to Zaditor. The study population included adults with a positive history of ocular allergies and/or positive skin reaction to cat hair, cat dander, grasses,

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ragweed and/or trees within 24 months of the screening visit (Visit 1) who manifested a positive allergen challenge at Visit 1 and confirmed at the baseline visit (Visit 2).

A total of 108 subjects were randomized to one of the following four treatment arms:

- Alaway + Alaway (n=33)
- Zaditor + Zaditor (n=30)
- Alaway + Vehicle (n=24)
- Zaditor + Vehicle (n=21)

The primary efficacy variable was ocular itching for each eye at 3, 5, and 7 minutes post-CAC at Visits 3 and 4. Ratings were made on a 0-4 scale, allowing half unit increments, where 0=none and 4.0=incapacitating itch with an irresistible urge to rub.

6.1.4 Efficacy Findings

Reference is made to the Agency's findings of efficacy in NDA 21-066.

STUDY ASI-003

Principle Investigators for Study ASI-003

Principal Investigator	Center	City and State	No. Randomized and Enrolled
Gail Torkildsen, M.D.	Ophthalmic Research Associates	Andover, MA	108

Inclusion Criteria:

To be eligible for the study, subjects must fulfill all of the following criteria:

1. Subjects must be willing to provide written informed consent.
2. Subjects must be able and willing to follow instructions.
3. Subjects must be able and willing to make the required study visits.
4. Subjects must be at least 18 years old, of either sex and any race.
5. Subjects must be willing to avoid certain medications and/or wearing contact lenses for 3 days prior to and for the duration of the study visit.
6. Subjects must manifest a successful allergen challenge (defined as $\geq 2+$ itching and $\geq 2+$ redness in at least two vessel beds) bilaterally at both Visit 1 and Visit 2.
7. Subjects must have a positive history of ocular allergies and a positive skin test reaction to cat hair, cat dander, ragweed, tree, and/or grass pollen within the last two years.
8. Subjects must have a calculated logMAR VA score (using the ETDRS chart) of 0.70 or better in each eye.

9. Subjects who are female and of child bearing potential (i.e. any female who had not had a hysterectomy, bilateral tubal ligation, or who had not been post-menopausal for at least two years), agreed to a urine pregnancy test at Visits 1 and 4 and agreed to use an approved method of birth control for the duration of the study. The results of pregnancy test at Visit 1 were negative.

Note: Approved methods of birth control included oral, implantable, transdermal, or injectable contraceptives, spermicide with barrier, or IUD. A woman using oral contraceptives must have been taking the medication regularly for 30 days prior to Visit 1; a woman using transdermal contraceptives must have been using the medication regularly for 7 days prior to Visit 1.

Exclusion Criteria:

Subjects meeting any of the following criteria will be excluded from the study:

1. Subjects who have any known contraindications or sensitivities to the use of any of the study medication(s).
2. Subjects who have a known allergy to the study medication(s) or their components.
3. Subjects who are women of child bearing potential who are:
 - Currently pregnant;
 - Currently nursing;
 - Currently planning a pregnancy;
 - Test positive to a urine pregnancy test at Visit 1; or
 - Refuse to use an approved method of contraception during the duration of the study.

Note: Approved methods of birth control include oral, implantable, transdermal, or injectable contraceptives, spermicide with barrier, or IUD. A woman using oral contraceptives must have been taking the medication regularly for 30 days prior to Visit 1; a woman using transdermal contraceptives must have been using the medication regularly for 7 days prior to Visit 1.

4. Subjects who have a presence of preauricular lymphadenopathy or any ocular condition that could affect study parameters (particularly, clinically significant blepharitis, follicular conjunctivitis, iritis).
5. Subjects who have a presence of an active bacterial or viral ocular infection.
6. Subjects who have a positive diagnosis of dry eye syndrome.
7. Subjects who use disallowed medications (systemic or topical ophthalmic) (i.e. H1-antagonist antihistamines, corticosteroids, mast cell stabilizers) during the appropriate pre-study washout period and during the study. H1-antagonist antihistamines may not be used within 3 days of Visit 1 or any time during the study. Any corticosteroid or mast cell stabilizer (including ocular) may not be used within 2 weeks of Visit 1 or any time during the study. Topical ophthalmic preparations (including tear substitutes), other than the study drops, may not be used within 72 hours of Visit 1 or any time during the study. The only exception is at each visit after the final CAC time point subjects may receive a

dose of a currently marketed, topical ophthalmic anti-allergic agent to relieve any immediate discomfort caused by the allergic reaction.

8. Subjects who have a presence of any significant illness that could be expected to interfere with the study parameters, such as any autoimmune disease, severe cardiovascular disease including arrhythmias, poorly controlled hypertension, or poorly controlled diabetes.
9. Subjects who manifest signs and symptoms of clinically active allergic conjunctivitis in either eye at the start of Visit 1, 2, 3, or 4 (greater than 1+ redness or the presence of any itching).
10. Subjects who have used an investigational drug or device within 30 days of the start of the study or who use an investigational drug or device during the study period (with the exception of this study medication).
11. Subjects who have a history or evidence of ocular surgery within the past 2 months.

Study Plan

This was a single-center, prospective, randomized, double-masked, active- and vehicle-controlled, conjunctival allergen challenge (CAC) study designed to show the bioequivalence of Alaway's formulation to Zaditor.

Subjects who met all inclusion/exclusion criteria and who manifested a positive allergen challenge at Visit 1 and confirmed at the baseline visit (Visit 2) were randomized to one of the following treatment arms:

- Alaway + Alaway
- Zaditor + Zaditor
- Alaway + Vehicle
- Zaditor + Vehicle

Subjects were administered on drop of masked study medication in each eye 8 hours prior to CAC at Visit 3 and 15 minutes prior to CAC at Visit 4. Ocular itching was assessed for each eye at 3, 5, and 7 minutes post-CAC at Visits 3 and 4.

Efficacy Endpoint

The primary efficacy variable was ocular itching for each eye at 3, 5, and 7 minutes post-CAC at Visits 3 (8 hours post-dosing) and 4 (15 minutes post-dosing). Ratings were made on a 0-4 scale, allowing half unit increments, where 0=none and 4.0=incapacitating itch with an irresistible urge to rub.

Patient Population

Disposition	Number of Subjects (Eyes) N=108 (216 eyes)			
	Alaway + Alaway	Alaway + Vehicle	Zaditor + Zaditor	Zaditor + Vehicle
Randomized	33 (66 eyes)	24 (48 eyes)	30 (60 eyes)	21 (42 eyes)
Completed	33 (66 eyes)	23 (46 eyes)	26 (52 eyes)	21 (42 eyes)
Safety Population	33 (66 eyes)	24 (48 eyes)	30 (60 eyes)	21 (42 eyes)
	Alaway	Zaditor	Vehicle	Total
Intent-to-Treat Population at Visit 3	90 eyes	81 eyes	45 eyes	108 (216 eyes)
Intent-to-Treat Population at Visit 4	89 eyes	73 eyes	44 eyes	103 (206 eyes)

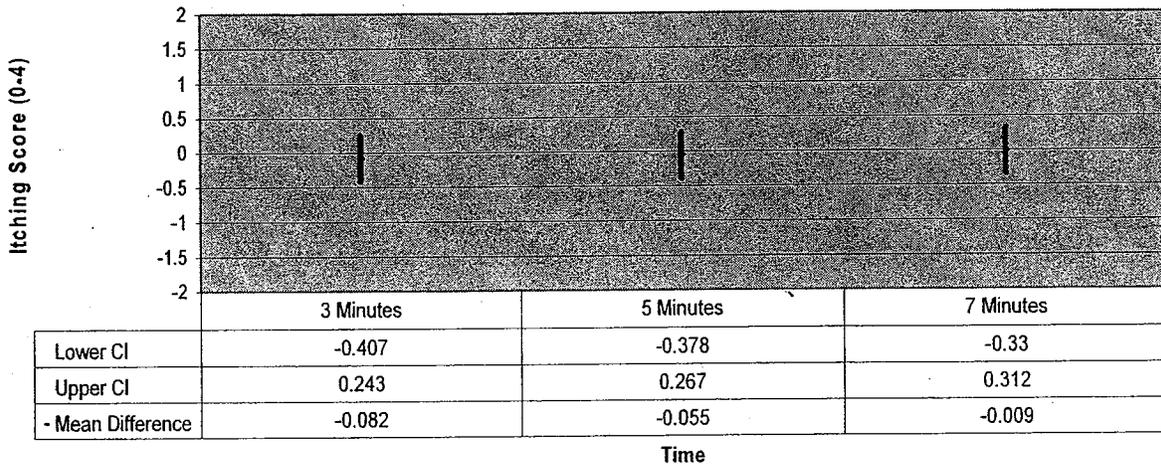
Ocular Itching Scores by Treatment at Visit 3 Post-CAC (8 Hours Post-Dosing Challenge)
 Intent-to-Treat Population

Time point	Treatment		
	Alaway (n=90)	Zaditor (n=81)	Vehicle (n=45)
3 minutes			
Mean	1.34	1.41	2.44
SD	1.040	1.013	0.867
Median	1.5	1.5	2.5
Range	(0.0, 4.0)	(0.0, 3.5)	(0.0, 3.5)
5 minutes			
Mean	1.37	1.43	2.59
SD	1.040	1.018	0.861
Median	1.0	1.5	2.5
Range	(0.0, 3.0)	(0.0, 3.5)	(0.5, 4.0)
7 minutes			
Mean	1.23	1.35	2.52
SD	1.036	1.044	0.866
Median	1.0	1.5	2.5
Range	(0.0, 3.0)	(0.0, 3.5)	(0.5, 4.0)
Itching assessed on a scale of 0-4, where 0=none and 4=severe			

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Clinical Review
Lucious Lim, M.D., M.P.H.
NDA 21-996 000
Alaway (ketotifen fumarate ophthalmic solution, 0.025%)

Mean Ocular Itching Score Difference (Alaway - Zaditor) with 95% Confidence Intervals - 8 Hours Post-Dosing Challenge



Reviewer's Comments: *The mean itching score of the two treatment arms is comparable. The 95% confidence interval crosses zero at all time points. The mean difference between the mean itching score of Alaway and Zaditor is less than 0.5 and not statistically significant at all time points. Alaway and Zaditor demonstrate equivalence in their ability to decrease ocular itching up to 8 hours post-dosing.*

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Clinical Review
 Lucious Lim, M.D., M.P.H.
 NDA 21-996 000
 Alaway (ketotifen fumarate ophthalmic solution, 0.025%)

Ocular Itching Scores by Treatment at Visit 4 Post-CAC (15 Minutes Post-Dosing Challenge)
 Intent-to-Treat Population

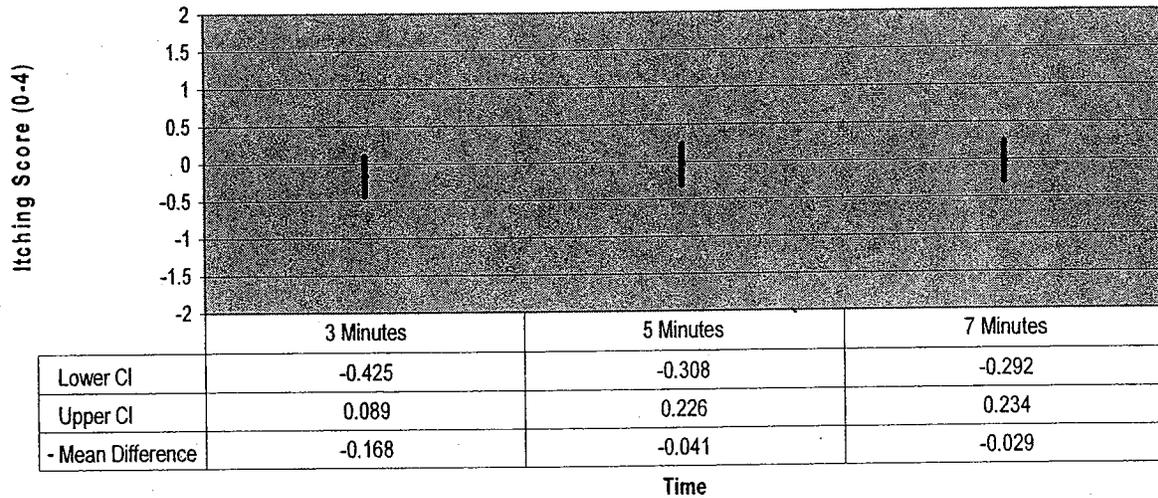
Timepoint	Treatment		
	Alaway (n=89)	Zaditor (n=73)	Vehicle (n=45)
3 minutes			
Mean	0.46	0.71	2.23
SD	0.632	0.837	0.866
Median	0.0	0.5	2.5
Range	(0.0, 2.5)	(0.0, 3.0)	(0.0, 4.0)
5 minutes			
Mean	0.61	0.72	2.33
SD	0.757	0.782	0.876
Median	0.5	0.5	2.5
Range	(0.0, 2.5)	(0.0, 3.0)	(0.0, 4.0)
7 minutes			
Mean	0.53	0.66	2.18
SD	0.667	0.795	0.947
Median	0.5	0.5	2.0
Range	(0.0, 2.5)	(0.0, 3.0)	(0.0, 3.5)
Itching assessed on a scale of 0-4, where 0=none and 4=severe			

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Clinical Review
Lucious Lim, M.D., M.P.H.
NDA 21-996 000
Alaway (ketotifen fumarate ophthalmic solution, 0.025%)

Mean Ocular Itching Score Difference (Alaway - Zaditor) with 95% Confidence Intervals - 15 Minutes Post-Dosing Challenge



Reviewer's Comments: *The mean itching score of the two treatment arms is comparable. The 95% confidence interval crosses zero at all time points. The mean difference between the mean itching score of Alaway and Zaditor is less than 0.5 and not statistically significant at all time points. Alaway and Zaditor demonstrate equivalence in their ability to decrease ocular itching at 15 minutes post-dosing.*

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ON ORIGINAL

6.1.5 Clinical Microbiology

There are no clinical microbiology related issues for this drug product. It is not an anti-infective.

6.1.6 Efficacy Conclusions

The bioequivalence of Alaway to Zaditor has been adequately demonstrated. This application supports the effectiveness of Alaway for the temporary relief of itching due to ragweed, pollen, grass, animal hair, and dander.

The major sources of clinical data in support of efficacy for Alaway utilized in this review include:

- Agency's efficacy findings in NDA 21-066 (Zaditor)
- Study ASI-003 (bioequivalence study comparing Alaway's formulation to Zaditor)

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

7.1.1 Deaths

No deaths occurred during the study.

7.1.2 Other Serious Adverse Events

Serious Adverse Events and Discontinued Patients for ASI-003

Treatment Group	Patient No.	Reason for Discontinuation	Comment
Zaditor + Zaditor	1007	Adverse event	Severe abdominal pain/torsion of right hemohydrosalpinx with hemoperitoneum

7.1.3 Dropouts and Other Significant Adverse Events

See Section 7.1.2

7.1.3.1 Overall profile of dropouts

Patient Disposition for Study ASI-003

	Alaway + Alaway N (eyes)	Alaway + Vehicle N (eyes)	Zaditor + Zaditor N (eyes)	Zaditor + Vehicle N (eyes)	Total N (eyes)
Screened					172 (344)
Randomized					108 (216)
Completed	33 (66)	23 (46)	26 (52)	21 (42)	103 (206)
Withdrew	0 (0)	1 (2)	4 (8)	0 (0)	5 (10)
Reason for withdrawal					
Adverse event			1 (2)		1 (2)
Exclusion criteria violation		1 (2)	2 (4)		3 (6)
Inclusion criteria violation			1 (2)		1 (2)

7.1.3.2 Adverse events associated with dropouts

A total of one subject discontinued from the study due to an adverse event. See section 7.1.2 for details.

7.1.3.3 Other significant adverse events

No other significant adverse event occurred during the study.

7.1.4 Other Search Strategies

Alimera prepared a listing of spontaneously reported adverse events associated with products containing ketotifen fumarate regardless of formulation or route of administration, prepared from a database purchased from the Uppsala Monitoring Centre, World Health Organization, Uppsala, Sweden. The database was generated in July 2005.

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

All adverse events either observed by the Investigator or one of his/her medical collaborators, or reported by the subject spontaneously, or in response to direct questioning were noted in the adverse events section of the subject's CRF and in the source document. Adverse events were elicited at each scheduled study visits after the screening and baseline visits.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

Adverse events were appropriately summarized by MedDRA body system and preferred term.

7.1.5.3 Incidence of common adverse events

One (1) ocular adverse event, abnormal eye sensation (4.2%) and two (2) non-ocular adverse events, nasopharyngitis (3.0%) and influenza (4.2%) were reported during the study.

7.1.5.4 Common adverse event tables

Frequency and Incidence of Ocular and Non-ocular Adverse Events
 Occurring at Rates 1% or Greater

Coded Adverse Event	Alaway + Alaway N=33 N (%)	Alaway + Vehicle N=24 N (%)	Zaditor + Zaditor N=30 N (%)	Zaditor + Vehicle N=21 N (%)
All Events	2 (6.0)	2 (8.3)	5 (16.7)	2 (9.5)
OCULAR				
Eye Disorder				
Abnormal sensation in eye		1 (4.2)		
NON-OCULAR				
Infections and Infestations				
Nasopharyngitis	1 (3.0)		2 (6.7)	
Ear infection			1 (3.3)	
Upper respiratory tract infection				1 (4.8)
Injury, Poisoning and Procedural Complications				
Joint pain	1 (3.0)			
Gastrointestinal Disorders				
Abdominal pain			1 (3.3)	
Nausea			1 (3.3)	
Nervous System Disorders				
Dizziness			2 (6.7)	
Respiratory, Thoracic and Mediastinal Disorders				
Influenza		1 (4.2)		

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 Lucious Lim, M.D., M.P.H.
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 Alaway (ketotifen fumarate ophthalmic solution, 0.025%)

Coded Adverse Event	Alaway + Alaway N=33	Alaway + Vehicle N=24	Zaditor + Zaditor N=30	Zaditor + Vehicle N=21
Pharyngolaryngeal pain			1 (3.3)	1 (4.8)
Sinus congestion			1 (3.3)	
Sneezing				1 (4.8)
Reproductive System and Breast Disorders				
Pelvic pain			1 (3.3)	

7.1.5.5 Identifying common and drug-related adverse events

None of the reported common adverse events appeared to be drug-related.

7.1.5.6 Additional analyses and explorations

No additional analyses and explorations were indicated and none were performed.

7.1.6 Less Common Adverse Events

No less common adverse events occurred during the study.

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

No laboratory assessments were performed.

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

See above.

7.1.7.3 Standard analyses and explorations of laboratory data

See above.

7.1.7.4 Additional analyses and explorations

See above.

7.1.7.5 Special assessments

There are no special laboratory assessments indicated for this drug product.

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

Vital signs assessment was not performed.

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

See above.

7.1.8.3 Standard analyses and explorations of vital signs data

See above.

7.1.8.4 Additional analyses and explorations

See above.

7.1.9 Electrocardiograms (ECGs)

7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

ECG testing was not performed.

7.1.9.2 Selection of studies and analyses for overall drug-control comparisons

See above.

7.1.9.3 Standard analyses and explorations of ECG data

See above.

7.1.9.4 Additional analyses and explorations

See above.

7.1.10 Immunogenicity

Reference is made to the Agency's non-clinical findings in NDA 21-066.

7.1.11 Human Carcinogenicity

Reference is made to the Agency's non-clinical findings in NDA 21-066.

7.1.12 Special Safety Studies

No special safety studies were performed or recommended for this drug product.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

No evidence of drug abuse or withdrawal phenomena has been reported for this drug product.

7.1.14 Human Reproduction and Pregnancy Data

There are no adequate and well-controlled studies in pregnant women.

7.1.15 Assessment of Effect on Growth

Safety and effectiveness in pediatric patients below the age of 3 years have not been established. There is no known effect on growth.

7.1.16 Overdose Experience

No information is available on overdosage in humans.

7.1.17 Postmarketing Experience

This is no postmarketing experience for this drug product. This is a new formulation and it has not been marketed in any country.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

The major sources of safety data in support of safety for Alaway in this review include:

- 1) Agency's findings of safety in NDA 21-066 (Zaditor)
- 2) An Alimera-prepared listing of postmarketing experiences compiled from a database generated in July 2005 by the Uppsala Monitoring Center, World Health Organization, Uppsala, Sweden

7.2.1.1 Study type and design/patient enumeration

See Section 4.2 of this review.

In addition, reference is made to Agency's findings of safety in NDA 21-066.

7.2.1.2 Demographics

Demographic Summary by Treatment Group for Study ASI-003

		Alaway + Alaway N=33	Alaway + Vehicle N=24	Zaditor + Zaditor N=30	Zaditor + Vehicle N=21
Age (years)	Mean	41/45	44.42	40.83	42.86
	SD	9.02	15.68	12.83	11.53
	Median	42.00	46.50	41.00	44.00
	Range	(18, 55)	(22, 85)	(18, 71)	(18, 62)
Gender – N (%)	Male	13 (39.4)	10 (41.7)	11 (36.7)	13 (61.9)
	Female	20 (60.6)	14 (58.3)	19 (63.3)	8 (38.1)
Race – N (%)	American Indian	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Asian	0 (0.0)	1 (4.2)	0 (0.0)	0 (0.0)
	Black	4 (12.1)	0 (0.0)	1 (3.3)	1 (4.8)
	White	28 (84.8)	22 (91.7)	29 (96.7)	20 (95.2)
	Other	1 (3.0)	1 (4.2)	0 (0.0)	0 (0.0)
Ethnicity – N (%)	Hispanic/Latino	3 (9.1)	1 (4.2)	0 (0.0)	0 (0.0)
	Not Hispanic/Latino	30 (90.0)	23 (95.8)	30 (100.0)	21 (100.0)
Iris Color –N (%)	Blue	12 (36.4)	8 (33.3)	10 (33.3)	2 (9.5)
	Brown	16 (48.5)	11 (45.8)	10 (33.3)	12 (57.1)
	Green	2 (6.1)	3 (12.5)	1 (3.3)	3 (14.3)
	Hazel	3 (9.1)	2 (8.3)	9 (30.0)	4 (19.0)

7.2.1.3 Extent of exposure (dose/duration)

A total of 57 patients (89 eyes) were exposed to the drug product in Study ASI-003. Each eye received one drop of Alaway at each of two study visits.

In addition, reference is made to the Agency's findings of safety in NDA 21-066.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

Alimera prepared a listing of postmarketing experiences compiled from a database generated in July 2005 by the Uppsala Monitoring Center, World Health Organization, Uppsala, Sweden.

In addition, reference is made to the Agency's findings of safety in NDA 21-066.

7.2.2.1 Other studies

See above.

7.2.2.2 Postmarketing experience

This is no postmarketing experience for this drug product. This is a new formulation and it has not been marketed in any country.

7.2.2.3 Literature

The literature references included in this submission are published reports on the safety and efficacy of Zaditor (NDA 21-066).

7.2.3 Adequacy of Overall Clinical Experience

The overall clinical experience is adequate.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

Reference is made to the Agency's non-clinical findings in NDA 21-066.

7.2.5 Adequacy of Routine Clinical Testing

Reference is made to the Agency's clinical findings in NDA 21-066.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

Reference is made to the Agency's non-clinical, clinical pharmacology, and clinical findings in NDA 21-066.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

There has been adequate evaluation for potential adverse events for this drug and for drugs in this class, and there are no recommendations for further study.

7.2.8 Assessment of Quality and Completeness of Data

The data submitted for the assessment of safety for Alaway is adequate and of good quality.

7.2.9 Additional Submissions, Including Safety Update

**Spontaneously Reported Adverse Events Reported for Products
 Containing Ketotifen Fumarate Regardless of Formulation or Route of Administration
 Occurring at Rates 1% or Greater**

Coded Adverse Event	Route of Administration				
	Number (%) of Patients				
	Ocular (N=22)	Oral (N=967)	Other Systemic (N=32)	Buccal (N=3)	Not Stated (N=25)
Total number of events	47	1594	64	8	61
OCULAR					
<u>Vision Disorders</u>					
Blepharitis			1 (3.1)		
Conjunctivitis	5 (22.7)				2 (8.0)
Diplopia			1 (3.1)		
Eye abnormality	1 (4.5)				
Eye pain	2 (9.1)				
Keratitis	1 (4.5)				
Thrombosis retinal vein			1 (3.1)		
NON-OCULAR					
<u>Body as a Whole-General Disorders</u>					
Allergic reaction			1 (3.1)		
Crying abnormal			1 (3.1)		
Death		12 (1.2)		1 (4.0)	
Fatigue		36 (3.7)		2 (8.0)	
Fever	2 (9.1)	10 (1.0)		1 (4.0)	
Influenza-like symptoms	2 (9.1)			2 (8.0)	
Malaise		13 (1.3)	1 (3.1)		
Medicine ineffective	1 (4.5)			3 (12.0)	
Oedema	1 (4.5)				
Oedema periorbital	2 (9.1)			1 (4.0)	
Rigors	2 (9.1)				1 (4.0)
Temperature changed sensation					1 (4.0)
Therapeutic response decreased		60 (6.2)			
<u>Cardiovascular Disorders - General</u>					
Circulatory failure					1 (4.0)
Cyanosis				1 (33.3)	
<u>Central & Peripheral Nervous System Disorders</u>					
Absences			1 (3.1)		
Convulsions			1 (3.1)		
Convulsions grand mal			1 (3.1)		
Dizziness	1 (4.5)	46 (4.8)	3 (9.1)		3 (12.0)
Dyskinesia			1 (3.1)		
EEG abnormal			1 (3.1)		
Fever convulsions			1 (3.1)		

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Headache	1 (4.5)	37 (3.8)			3 (12.0)
Hyperkinesia		13 (1.3)	1 (3.1)	1 (33.3)	
Hypoaesthesia					1 (4.0)
Paraesthesia	1 (4.5)				1 (4.0)
Tremor		10 (1.0)	1 (3.1)		
Vertigo		10 (1.0)			
<u>Endocrine Disorders</u>					
Gynaecomastia			2 (6.3)		1 (4.0)
<u>Gastrointestinal System Disorders</u>					
Abdominal pain		15 (1.6)	1 (3.1)		
Colitis			1 (3.1)		
Constipation		10 (1.0)			
Diarrhoea		26 (2.7)	2 (6.3)		
Dyspepsia					1 (4.0)
Gingivitis					1 (4.0)
Haematemesis			1 (3.1)		
Ileus			1 (3.1)		
Mouth dry		20 (2.1)			
Nausea		41 (4.2)	2 (6.3)		3 (12.0)
Tongue disorder					1 (4.0)
Vomiting		28 (2.9)	2 (6.3)		2 (8.0)
<u>Hearing and Vestibular Disorders</u>					
Ear disorder nos	1 (4.5)				
<u>Heart Rate and Rhythm Disorders</u>					
Tachycardia		16 (1.7)		1 (33.3)	
<u>Metabolic and Nutritional Disorders</u>					
Phosphatase alkaline increased			1 (3.1)		
Thirst	1 (4.5)				
Weight increase		35 (3.6)	7 (21.9)		2 (8.0)
<u>Musculoskeletal System Disorders</u>					
Arthralgia	1 (4.5)		2 (6.3)		2 (8.0)
Arthrosis			1 (3.1)		
Fracture pathological			1 (3.1)		
Myalgia				1 (33.3)	1 (4.0)
<u>Myo-, Endo-, Pericardial & Valve Disorders</u>					
Myocardial infraction		16 (1.7)			
<u>Platelet, Bleeding & Clotting Disorders</u>					
Thrombocytopenia			2 (6.3)		
<u>Psychiatric Disorders</u>					
Aggressive reaction		25 (2.6)			
Agitation		27 (2.8)			
Anorexia			1 (3.1)		
Appetite increased			5 (15.6)		
Depersonalization					1 (4.0)
Depression		21 (2.2)	2 (6.3)		1 (4.0)

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Emotional lability			1 (3.1)		
Hallucination		10 (1.0)			
Insomnia		11 (1.1)	1 (3.1)	1 (33.3)	
Manic reaction			1 (3.1)		
Nervousness		33 (3.4)			1 (4.0)
Paroniria					1 (4.0)
Personality disorder					1 (4.0)
Somnolence	1 (4.5)	222 (23.0)	1 (3.1)		4 (16.0)
Thinking abnormal			1 (3.1)		
Reproductive Disorders - Female					
Menstrual disorder			2 (6.3)	1 (33.3)	
Resistance Mechanism Disorders					
Wound dehiscence			1 (3.1)		
Respiratory System Disorders					
Atelectasis					1 (4.0)
Bronchospasm		10 (1.0)	1 (3.1)		
Bronchospasm aggravated		48 (5.0)			1 (4.0)
Dyspnoea	1 (4.5)	11 (1.1)		1 (33.3)	1 (4.0)
Epistaxis				1 (33.3)	
Laryngitis	1 (4.5)				
Pharyngitis	2 (9.1)				1 (4.0)
Pneumonia	1 (4.5)				1 (4.0)
Respiratory insufficiency					1 (4.0)
Rhinitis	2 (9.1)				
Skin and Appendages Disorders					
Alopecia		12 (1.2)			1 (4.0)
Dermatitis contact	5 (22.7)				
Dermatitis exfoliative	1 (4.5)				
Pruritus	3 (13.6)	16 (1.7)	1 (3.1)		2 (8.0)
Rash		29 (3.0)			1 (4.0)
Rash erythematous		15 (1.6)			
Rash follicular			1 (3.1)		
Sweating increased		11 (1.1)			
Urticaria		18 (1.9)			
Urinary Systemic Disorders					
Cystitis		11 (1.1)			
Face oedema		11 (1.1)			
Haematuria			1 (3.1)		
Polyuria					1 (4.0)
Urinary incontinence		11 (1.1)			
Vascular (Extracardiac) Disorders					
Vasculitis			1 (3.1)		
White Cell and Resistance Disorders					
Leukocytosis	1 (4.5)				1 (4.0)

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

See tables in Section 7.1.5.4 and Section 7.2 of this review.

7.4 General Methodology

Reference is made to the Agency's findings of safety in NDA 21-066.

A bioequivalence study (ASI-003) was conducted comparing Alaway to Zaditor. See Section 7.1.5.4 for the safety findings from this study.

8 ADDITIONAL CLINICAL ISSUES

There are no additional clinical issues.

8.1 Dosing Regimen and Administration

See above.

8.2 Drug-Drug Interactions

See above.

8.3 Special Populations

See above.

8.4 Pediatrics

Reference is made the Agency's finding of safety and effectiveness in pediatric patients below the age of 3 years in NDA 21-066.

Alimera has requested a waiver to conduct pediatric studies.

8.5 Advisory Committee Meeting

On December 17, 1990, the Ophthalmic Subcommittee of the Anti-Infective Advisory Committee recommended that products to treat allergic conjunctivitis be made available without a prescription.

8.6 Literature Review

See Section 7.2.1.3 of this review.

8.7 Postmarketing Risk Management Plan

There are no recommended Phase 4 clinical study commitments.

8.8 Other Relevant Materials

There are no other relevant materials.

9 OVERALL ASSESSMENT

9.1 Conclusions

The safety and efficacy of Alaway for the temporary relief of itchy eye due to ragweed, pollen, grass, animal hair, and dander in adults and children 3 years and older has adequately been demonstrated.

9.2 Recommendation on Regulatory Action

It is recommended that NDA 21-996 be approved for over-the-counter use with the labeling revisions listed in this review.

The application supports the safety and effectiveness of — for the temporary relief of itchy eye due to ragweed, pollen, grass, animal hair, and dander.

There are no recommendations for additional postmarketing studies.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

There are no recommended Phase 4 clinical study commitments.

9.3.2 Required Phase 4 Commitments

There are no recommended Phase 4 clinical study commitments.

9.3.3 Other Phase 4 Requests

There are no optional or recommended Phase 4 requests.

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NDA 21-996 000
Alaway (ketotifen fumarate ophthalmic solution, 0.025%)

9.4 Labeling Review

See the Line-by-Line Labeling review, Section 10.2.

9.5 Comments to Applicant

There are no comments to be conveyed to the applicant.

**APPEARS THIS WAY
ON ORIGINAL**

10 APPENDICES

10.1 Review of Individual Study Reports

See Section 6.1 of this review.

10.2 Line-by-Line Labeling Review

Following is Alimera's proposed labeling submitted with the original New Drug Application on January 31, 2006.

Reviewer's proposed deletions are noted by and additions by underline within the following labeling.

4 Page(s) Withheld

 § 552(b)(4) Trade Secret / Confidential

X § 552(b)(4) Draft Labeling

 § 552(b)(5) Deliberative Process

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

/s/

Lucious Lim
10/4/2006 11:12:17 AM
MEDICAL OFFICER

William Boyd
10/4/2006 12:02:28 PM
MEDICAL OFFICER

M.O. Review #2
Labeling Amendment to Original NDA 21-996

Submitted: June 28, 2006; August 18, 2006; October 12, 2006;
October 20, 2006; October 26, 2006; November 1,
2006

Received: June 30, 2006; August 21, 2006; October 16, 2006;
October 23, 2006; October 30, 2006; November 3,
2006

Review completed: November 8, 2006

Reviewer: Lucious Lim, M.D., M.P.H.

Proposed Tradename: Alaway

Established Name: Ketotifen 0.025% (equivalent to ketitofen fumarate
0.035%)

Applicant: Alimera Sciences, Inc.
6120 Windward Parkway, Suite 290
Alpharetta, GA 30005
(678) 527-1330
Contact: Barbara H. Bauschka

Pharmacologic Category: Antihistamine

Proposed Indication: Temporary relief of itchy eyes due to ragweed,
pollen, grass, animal hair and dander

**Dosage Form and
Route of Administration:** Ophthalmic solution for topical administration

Submitted:

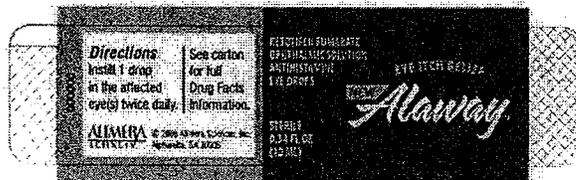
Submitted are revised final labeling (Drug Facts and container and carton labeling) based on previous review and discussion with the applicant.

Reviewer's Comments:

The sponsor has accepted all changes to the labeling as requested by the Division. The submitted labeling (Drug Facts and container and carton labeling) is acceptable

Final Drug Facts and Container and Carton Labeling, Submitted November 1, 2006

Container Label



**APPEARS THIS WAY
ON ORIGINAL**

Drug Facts and Carton Label

M.O. Review #2
NDA 21-996 Alaway (ketotifen 0.025%)
Reviewer: Lucious Lim, M.D., M.P.H.

Lucious Lim, M.D., M.P.H.
Medical Officer

cc: HFD-520/Div Files
HFD-520/PM/Rodgers
HFD-520/Chem/Qi
HFD-520/MO/Lim
HFD-520/CTL/Boyd
HFD-520/Dep Div Dir/Chambers

M.O. Review #2
NDA 21-996 Alaway (ketotifen 0.025%)
Reviewer: Lucious Lim, M.D., M.P.H.

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

/s/

Lucious Lim
11/8/2006 03:04:45 PM
MEDICAL OFFICER

William Boyd
11/8/2006 03:10:51 PM
MEDICAL OFFICER