

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21-996**

**ADMINISTRATIVE and CORRESPONDENCE  
DOCUMENTS**



**For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.**

**2. Drug Substance (Active Ingredient)**

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?  Yes  No

2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?  Yes  No

2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).  Yes  No

2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.

2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)  Yes  No

2.6 Does the patent claim only an intermediate?  Yes  No

2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)  Yes  No

**3. Drug Product (Composition/Formulation)**

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?  Yes  No

3.2 Does the patent claim only an intermediate?  Yes  No

3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)  Yes  No

**4. Method of Use:**

**Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:**

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?  Yes  No

4.2 Claim Number (as listed in the patent) Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?  Yes  No

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product. Use: (Submit indication or method of use information as identified specifically in the proposed labeling.)

**5. No Relevant Patents**

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.  Yes

**6: Declaration Certification**

6.1 The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.

**Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.**

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)

*Susan H. Caballa*

Date Signed

03/30/2006

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

NDA Applicant/Holder

NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official

Patent Owner

Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

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The public reporting burden for this collection of information has been estimated to average 9 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration  
CDER (HFD-007)  
5600 Fishers Lane  
Rockville, MD 20857

*An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.*

## EXCLUSIVITY SUMMARY

NDA # 21-996

SUPPL #

HFD # 520

Trade Name Alaway

Generic Name ketotifen fumarate ophthalmic solution

Applicant Name Alimera Sciences, Inc.

Approval Date, If Known 12-1-2006

### PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES  NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)(2)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES  NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES  NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES  NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES  NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

## PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES  NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 21-996

Zaditor

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES  NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)

IF "YES," GO TO PART III.

**PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS**

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of

summary for that investigation.

YES  NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES  NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES  NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES  NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES  NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1

YES  NO

Investigation #2

YES  NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1

YES  NO

Investigation #2

YES  NO



Investigation #1  
!  
!  
YES  ! NO   
Explain: ! Explain:

Investigation #2  
!  
!  
YES  ! NO   
Explain: ! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES  NO

If yes, explain:

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Name of person completing form: Alison Rodgers  
Title: Project Manager  
Date: 12-5-06

Name of Office/Division Director signing form: Wiley Chambers, M.D.  
Title: Deputy Director, Division of Anti-Infective and Ophthalmology Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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

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Wiley Chambers  
12/12/2006 08:17:24 AM

**PEDIATRIC PAGE**

(Complete for all filed original applications and efficacy supplements)

NDA/BLA #: 21-996 Supplement Type (e.g. SE5): \_\_\_\_\_ Supplement Number: \_\_\_\_\_

Stamp Date: January 31, 2006 PDUFA Goal Date: December 1, 2006

HFD 520 Trade and generic names/dosage form: Alaway (ketotifen fumarate ophthalmic solution), 0.025%

Applicant: Alimera Sciences, Inc. Therapeutic Class: Antihistamine

Does this application provide for new active ingredient(s), new indication(s), new dosage form, new dosing regimen, or new route of administration? \*

- Yes. Please proceed to the next question.
- No. PREA does not apply. Skip to signature block.

\* SE5, SE6, and SE7 submissions may also trigger PREA. If there are questions, please contact the Rosemary Addy or Grace Carmouze.

Indication(s) previously approved (please complete this section for supplements only): \_\_\_\_\_

Each indication covered by current application under review must have pediatric studies: *Completed, Deferred, and/or Waived.*

Number of indications for this application(s): \_\_\_\_\_

Indication #1: \_\_\_\_\_

Is this an orphan indication?

- Yes. PREA does not apply. Skip to signature block.
- No. Please proceed to the next question.

Is there a full waiver for this indication (check one)?

- Yes: Please proceed to Section A.
- No: Please check all that apply:  Partial Waiver  Deferred  Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

**Section A: Fully Waived Studies**

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Other: \_\_\_\_\_

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

NDA 

Page 3

**This page was completed by:**

*{See appended electronic signature page}*

**Alison Rodgers**

**Regulatory Project Manager**

**FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH  
STAFF at 301-796-0700**

**(Revised: 10/10/2006)**

**APPEARS THIS WAY  
ON ORIGINAL**

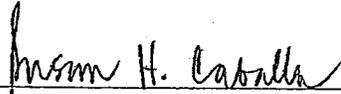
-----  
**This is a representation of an electronic record that was signed electronically and  
this page is the manifestation of the electronic signature.**  
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/s/

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Alison Rodgers  
12/5/2006 09:40:38 AM

Debarment Certification

Alimera Sciences, Inc. hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this New Drug Application for ketotifen fumarate ophthalmic solution, 0.025%, NDA 21-966.



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Susan H. Caballa

Vice-President, Regulatory and Medical Affairs

**APPEARS THIS WAY  
ON ORIGINAL**

**Deputy Division Director Memorandum**

Application Type	NDA 21-996
Letter Date	January 31, 2006
Review Completion Date	November 22, 2006
Established Name	Ketotifen fumarate ophthalmic solution
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

**Recommendation on Regulatory Action**

It is recommended that NDA 21-996 be approved for over-the-counter use with the labeling submitted on November 1, 2006.

The application supports the safety and effectiveness of Alaway for the temporary relief of itchy eyes due to ragweed, pollen, grass, animal hair and dander. NDA 21-996 relies on the findings of NDA 21-066 and it is recommended that the labeling between the two NDAs be consistent.

There are no recommendations for additional postmarketing studies.

**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.

**Required Phase 4 Commitments**

There are no recommended Phase 4 clinical study commitments.

## Brief Overview of Clinical Program

Ketotifen fumarate ophthalmic solution, 0.025% (Zaditor) is an approved drug product for over the counter use in the United States. Zaditor (NDA 21-066) was approved on July 2, 1999, as a prescription only drug product for the temporary prevention of itching of the eye due to allergic conjunctivitis. On October 19, 2006, Zaditor's labeling was changed to remove the prescription only restriction.

Alaway is an ophthalmic solution containing ketotifen fumarate ophthalmic solution, 0.025% and is proposed to be marketed for the temporary relief of itchy eyes due to ragweed, pollen, grass, animal hair and dander. The application references the Agency's prior findings of safety and efficacy in NDA 21-066 to support the safety and effectiveness of Alaway. The only difference between the formulations of Zaditor and Alaway is \_\_\_\_\_  
\_\_\_\_\_  
Alimera, Inc. conducted a clinical bioequivalence study and demonstrated the clinical bioequivalence of the \_\_\_\_\_ formulation to Zaditor.

## OTC Background

On December 17, 1990, the Anti-Infective Advisory Committee, Sub-committee on Ophthalmic Drugs (Advisory Committee) met to discuss whether products indicated for allergic conjunctivitis would be appropriate for OTC use. There was the clear consensus by the Advisory Committee, in concurrence with the petitioner's first point, that allergic conjunctivitis is a diagnosis that cannot be accurately made by members of the public, nor for that matter, reliably made by physicians.

However, the Advisory Committee concluded that ocular itching and/or ocular redness, symptoms that are characteristic of allergic conjunctivitis, could be identifiable by consumers without medical training. Therefore, the Advisory Committee recommended that topical ophthalmic antihistamine/vasoconstrictor combinations could be marketed OTC for the treatment of ocular itching and redness.

FDA agreed with the Advisory Committee and subsequently approved for OTC use several topical ophthalmic antihistamine/vasoconstrictor combinations (e.g., Vasocon-A (NDA 18-746, July 11, 1994), Naphcon-A (NDA 20-226, June 8, 1994), Opcon-A (20-065, June 8, 1994). These OTC products were approved for the treatment of ocular itching and redness due to pollen, ragweed, grass, animal hair, and dander. Although a single ingredient antihistamine, similar to these products, Zaditor has been shown in clinical studies to be safe and effective for the treatment of ocular itching for those same allergens and Alaway is considered to be bioequivalent to Zaditor.

## 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 — were the Agency's findings of efficacy in NDA 21-066 and Study ASI-003 (bioequivalence study comparing Alaway's formulation to Zaditor).

### **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 — include the Agency's findings of safety in NDA 21-066, and 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.

No safety issues have been identified with the — concentration of glycerin — in this formulation.

### **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.

### **Drug-Drug Interactions**

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

### **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.

Although there is data to support the safety of the ketotifen fumarate ophthalmic solution below the age of 3 years old, safety and effectiveness in pediatric patients below the age of 3 years have not been established because of the difficulty in reliably identifying the indication below the age of 3.

## ACTION PACKAGE CHECKLIST

Application Information		
BLA # NDA # 21-996	BLA STN# NDA Supplement #	If NDA, Efficacy Supplement Type
Proprietary Name: Alaway Established Name: ketotifen fumarate Dosage Form: ophthalmic solution		Applicant: Alimera Sciences, Inc.
RPM: Alison Rodgers		Division: Anti-Infective and Ophthalmology Products Phone # 301-796-0797
NDAs: NDA Application Type: <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)  (A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)		505(b)(2) NDAs and 505(b)(2) NDA supplements: Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)):  NDA 21-066, Zaditor  Provide a brief explanation of how this product is different from the listed drug. Change from RX to OTC.  <input type="checkbox"/> If no listed drug, check here and explain:  <b>Review and confirm the information previously provided in Appendix B to the Regulatory Filing Review. Use this Checklist to update any information (including patent certification information) that is no longer correct.</b>  <input checked="" type="checkbox"/> Confirmed <input type="checkbox"/> Corrected Date: 11-9-06
❖ User Fee Goal Date		12-1-06
❖ Action Goal Date (if different)		12-1-06
❖ Actions		
• Proposed action		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> AE <input type="checkbox"/> NA <input type="checkbox"/> CR
• Previous actions (specify type and date for each action taken)		<input checked="" type="checkbox"/> None
❖ Advertising (approvals only) Note: If accelerated approval (21 CFR 314.510/601.41), advertising must have been submitted and reviewed (indicate dates of reviews)		<input checked="" type="checkbox"/> Requested in AP letter <input type="checkbox"/> Received and reviewed

❖ Application Characteristics	
Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority Chemical classification (new NDAs only): 8	
NDAs, BLAs and Supplements: <input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> CMA Pilot 1 <input type="checkbox"/> CMA Pilot 2  <input type="checkbox"/> Orphan drug designation	
NDAs: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) Subpart I <input type="checkbox"/> Approval based on animal studies	BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 601.41) <input type="checkbox"/> Restricted distribution (21 CFR 601.42) Subpart H <input type="checkbox"/> Approval based on animal studies
NDAs and NDA Supplements: <input type="checkbox"/> OTC drug	
Other:  Other comments:	
❖ Application Integrity Policy (AIP)	
<ul style="list-style-type: none"> <li>Applicant is on the AIP</li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> <li>This application is on the AIP                             <ul style="list-style-type: none"> <li>Exception for review (<i>file Center Director's memo in Administrative Documents section</i>)</li> <li>OC clearance for approval (<i>file communication in Administrative Documents section</i>)</li> </ul> </li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No  <input type="checkbox"/> Yes <input type="checkbox"/> No  <input type="checkbox"/> Yes <input type="checkbox"/> Not an AP action
❖ Public communications (approvals only)	
<ul style="list-style-type: none"> <li>Office of Executive Programs (OEP) liaison has been notified of action</li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> <li>Press Office notified of action</li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> <li>Indicate what types (if any) of information dissemination are anticipated</li> </ul>	<input checked="" type="checkbox"/> None <input type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other

<p>❖ <b>Exclusivity</b></p>	
<ul style="list-style-type: none"> <li>• NDAs: Exclusivity Summary (approvals only) (<i>file Summary in Administrative Documents section</i>)</li> </ul>	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> <li>• Is approval of this application blocked by any type of exclusivity?</li> <li>• NDAs/BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? <i>Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</i></li> <li>• NDAs: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? (<i>Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.</i>)</li> <li>• NDAs: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (<i>Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.</i>)</li> <li>• NDAs: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? (<i>Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.</i>)</li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes  <input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA #            and date exclusivity expires:  <input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA #            and date exclusivity expires:  <input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA #            and date exclusivity expires:
<p>❖ <b>Patent Information (NDAs and NDA supplements only)</b></p>	
<ul style="list-style-type: none"> <li>• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.</li> </ul>	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> <li>• Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.</li> <li>• [505(b)(2) applications] If the application includes a <b>paragraph III</b> certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).</li> </ul>	21 CFR 314.50(i)(1)(i)(A) <input checked="" type="checkbox"/> Verified  21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)  <input type="checkbox"/> No paragraph III certification Date patent will expire
<ul style="list-style-type: none"> <li>• [505(b)(2) applications] For each <b>paragraph IV</b> certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). (<i>If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (Summary Reviews).</i>)</li> <li>• [505(b)(2) applications] For each <b>paragraph IV</b> certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.</li> </ul> <p>Answer the following questions for each paragraph IV certification:</p> <p>(1) Have 45 days passed since the patent owner's receipt of the applicant's</p>	<input type="checkbox"/> N/A (no paragraph IV certification) <input checked="" type="checkbox"/> Verified          <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No

notice of certification?

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

If "Yes," skip to question (4) below. If "No," continue with question (2).

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

Yes  No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "No," continue with question (3).

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes  No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes  No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "No," continue with question (5).

- (5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?

Yes  No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced

<p>within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.</i></p>	
<b>Summary Reviews</b>	
<p>❖ Summary Reviews (e.g., Office Director, Division Director) (indicate date for each review)</p>	
<p>❖ BLA approvals only: Licensing Action Recommendation Memo (LARM) (indicate date)</p>	
<b>Labeling</b>	
<p>❖ Package Insert</p>	
<ul style="list-style-type: none"> <li>• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)</li> </ul>	
<ul style="list-style-type: none"> <li>• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)</li> </ul>	
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> <li>• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable</li> </ul>	
<p>❖ Patient Package Insert</p>	
<ul style="list-style-type: none"> <li>• Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling)</li> </ul>	
<ul style="list-style-type: none"> <li>• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)</li> </ul>	
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> <li>• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable</li> </ul>	
<p>❖ Medication Guide</p>	
<ul style="list-style-type: none"> <li>• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)</li> </ul>	
<ul style="list-style-type: none"> <li>• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)</li> </ul>	
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> <li>• Other relevant labeling (e.g., most recent 3 in class, class labeling)</li> </ul>	
<p>❖ Labels (full color carton and immediate-container labels)</p>	
<ul style="list-style-type: none"> <li>• Most-recent division-proposed labels (only if generated after latest applicant submission)</li> </ul>	N/A
<ul style="list-style-type: none"> <li>• Most recent applicant-proposed labeling</li> </ul>	11-1-06 (2)
<p>❖ Labeling reviews and minutes of any labeling meetings (indicate dates of reviews and meetings)</p>	<input checked="" type="checkbox"/> DMETS 9-1-06; 5-31-06 <input type="checkbox"/> DSRCS <input type="checkbox"/> DDMAC <input type="checkbox"/> SEALD <input checked="" type="checkbox"/> Other reviews 11-8-06; OTC - 11-2-06; 9-22-06 (3) <input type="checkbox"/> Memos of Mtgs

Administrative Documents	
❖ Administrative Reviews (RPM Filing Review/Memo of Filing Meeting; ADRA) ( <i>indicate date of each review</i> )	10-24-06
❖ NDA and NDA supplement approvals only: Exclusivity Summary ( <i>signed by Division Director</i> )	<input checked="" type="checkbox"/> Included
❖ AIP-related documents <ul style="list-style-type: none"> <li>Center Director's Exception for Review memo</li> <li>If AP: OC clearance for approval</li> </ul>	N/A
❖ Pediatric Page (all actions)	<input checked="" type="checkbox"/> Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent. ( <i>Include certification.</i> )	<input checked="" type="checkbox"/> Verified, statement is acceptable
❖ Postmarketing Commitment Studies <ul style="list-style-type: none"> <li>Outgoing Agency request for post-marketing commitments (<i>if located elsewhere in package, state where located</i>)</li> <li>Incoming submission documenting commitment</li> </ul>	<input checked="" type="checkbox"/> None
❖ Outgoing correspondence (letters including previous action letters, emails, faxes, telecons)	11-1-06; 9-25-06; 9-18-06; 8-29-06; 8-28-06; 4-14-06; 4-3-06; 3-1-06
❖ Internal memoranda, telecons, email, etc.	9-20-06
❖ Minutes of Meetings <ul style="list-style-type: none"> <li>Pre-Approval Safety Conference (<i>indicate date; approvals only</i>)</li> <li>Pre-NDA/BLA meeting (<i>indicate date</i>)</li> <li>EOP2 meeting (<i>indicate date</i>)</li> <li>Other (e.g., EOP2a, CMC pilot programs)</li> </ul>	N/A <input checked="" type="checkbox"/> No mtg <input checked="" type="checkbox"/> No mtg Pre-IND 6-25-04
❖ Advisory Committee Meeting <ul style="list-style-type: none"> <li>Date of Meeting</li> <li>48-hour alert or minutes, if available</li> </ul>	<input checked="" type="checkbox"/> No AC meeting
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	N/A
CMC/Product Quality Information	
❖ CMC/Product review(s) ( <i>indicate date for each review</i> )	11-7-06
❖ Reviews by other disciplines/divisions/Centers requested by CMC/product reviewer ( <i>indicate date for each review</i> )	<input type="checkbox"/> None
❖ BLAs: Product subject to lot release (APs only)	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Environmental Assessment (check one) (original and supplemental applications) <ul style="list-style-type: none"> <li><input checked="" type="checkbox"/> Categorical Exclusion (<i>indicate review date</i>)(<i>all original applications and all efficacy supplements that could increase the patient population</i>)</li> <li><input type="checkbox"/> Review &amp; FONSI (<i>indicate date of review</i>)</li> <li><input type="checkbox"/> Review &amp; Environmental Impact Statement (<i>indicate date of each review</i>)</li> </ul>	11-7-06
❖ NDAs: Microbiology reviews (sterility & apyrogenicity) ( <i>indicate date of each review</i> )	9-25-06 <input type="checkbox"/> Not a parenteral product
❖ Facilities Review/Inspection <ul style="list-style-type: none"> <li>NDAs: Facilities inspections (include EER printout)</li> </ul>	Date completed: 3-17-06 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation

❖ BLAs: Facility-Related Documents <ul style="list-style-type: none"> <li>• Facility review (<i>indicate date(s)</i>)</li> <li>• Compliance Status Check (approvals only, both original and supplemental applications) (<i>indicate date completed, must be within 60 days prior to AP</i>)</li> </ul>	<input type="checkbox"/> Requested <input type="checkbox"/> Accepted <input type="checkbox"/> Hold
❖ NDAs: Methods Validation	<input checked="" type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed
<b>Nonclinical Information</b>	
❖ Pharm/tox review(s), including referenced IND reviews ( <i>indicate date for each review</i> )	5-17-06; 3-17-06
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	
❖ Nonclinical inspection review Summary (DSI)	<input checked="" type="checkbox"/> None requested
<b>Clinical Information</b>	
❖ Clinical review(s) ( <i>indicate date for each review</i> )	10-4-06
❖ Financial Disclosure reviews(s) or location/date if addressed in another review	
❖ Clinical consult reviews from other review disciplines/divisions/Centers ( <i>indicate date of each review</i> )	<input checked="" type="checkbox"/> None
❖ Microbiology (efficacy) reviews(s) ( <i>indicate date of each review</i> )	<input checked="" type="checkbox"/> Not needed
❖ Safety Update review(s) ( <i>indicate location/date if incorporated into another review</i> )	
❖ Risk Management Plan review(s) (including those by OSE) ( <i>indicate location/date if incorporated into another review</i> )	N/A
❖ Controlled Substance Staff review(s) and recommendation for scheduling ( <i>indicate date of each review</i> )	<input checked="" type="checkbox"/> Not needed
❖ DSI Inspection Review Summary(ies) ( <i>include copies of DSI letters to investigators</i> )	<input type="checkbox"/> None requested
• Clinical Studies	10-25-06
• Bioequivalence Studies	
• Clin Pharm Studies	
❖ Statistical Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
❖ Clinical Pharmacology review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None

## Appendix A to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

- (1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
- (2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
- (3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
- (2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
- (3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication **AND** a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
- (2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
- (3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's Office of Regulatory Policy representative.

OTC Drug Labeling Review Addendum  
Alaway™ Ophthalmic Solution, 0.025%

Office of Nonprescription Products  
Center for Drug Evaluation and Research • Food and Drug Administration

**NDA 21-996**

**SUBMISSION DATES:** October 5 and 27, 2006  
November 1, 2006

**REVIEW DATE:** November 2, 2006

**SPONSOR CONTACT:** Alimera Sciences  
Barbara H. Bauschka  
Manager, Regulatory Affairs  
1-678-527-1330

**DRUG PRODUCT:** Alaway™ Ophthalmic Solution, 0.025%

**ACTIVE INGREDIENT:** Ketotifen fumarate 0.035% (equivalent to ketotifen 0.025%)

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

**PHARMACOLOGIC CATEGORY:** Antihistamine

**LABELING SUBMITTED:** Carton and container labels – 10 mL

**BACKGROUND:** On October 17, 2006, Agency representatives provided feedback on Sponsor's labeling submission of October 5, 2006 in a teleconference feedback communication. On October 26, 2006, Sponsor submitted revised proposed labeling. In an October 27, 2006 teleconference with the Sponsor, Agency representatives suggested additional revisions.

**REVIEWER'S COMMENT:** As stated in Project Management's e-mail date of October 25, 2006, the Sponsor no longer plans to use the insert with the "Drug Facts"

The Sponsor has made acceptable changes to the labeling as suggested by Agency representatives in their latest feedback teleconference communication.

**RECOMMENDATIONS:**

1. An "APPROVAL" can be issued to the Sponsor requesting final printed labeling identical to the draft labeling submitted on November 1, 2006.

2. Inform the Sponsor that the flag "NEW" must be deleted from the principal display, right, and top panels, six months after introduction of the product into the OTC marketplace.

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Michael T. Benson, R.Ph., J.D.  
Regulatory Review Pharmacist

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Marina Chang, R.Ph. Concurrence  
Leader, Team #1

**APPEARS THIS WAY  
ON ORIGINAL**

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

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Michael Benson  
11/2/2006 02:02:00 PM  
INTERDISCIPLINARY

Marina Chang  
11/2/2006 02:12:07 PM  
INTERDISCIPLINARY

# ALIMERA SCIENCES

November 1, 2006

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Anti-Infective and Ophthalmology Products  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

**Re: NDA 21-996**  
**Ketotifen Fumarate Ophthalmic Solution, 0.025%**  
**Amendment: Draft Labeling Response – Mock-ups**

Dear Sir or Madam:

Alimera Sciences, Inc. is providing mock-ups of the carton and label for Alaway in response to the emails of October 5, 2006 and October 27, 2006 as well as in response to the discussions of the teleconferences with the Agency on October 17, 2006 and October 27, 2006 regarding Draft Labeling.

If you have any questions or need additional information, please contact me via email or by telephone at 678-527-1330.

Sincerely,

*Barbara H. Bauschka*

Barbara H. Bauschka  
Manager, Regulatory Affairs  
barbara.bauschka@alimerasciences.com

# ALIMERA SCIENCES

October 26, 2006

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Anti-Infective and Ophthalmology Products  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

**Re: NDA 21-996**  
**Ketotifen Fumarate Ophthalmic Solution, 0.025%**  
**Amendment: Draft Labeling Response**

Dear Sir or Madam:

Upon further review, Alimera Sciences, Inc. is providing additional responses to the email of October 5, 2006 and results of the teleconference with the Agency on October 17, 2006 on the Draft Labeling for Alaway. This response includes alternative wording that conveys the same basic information but using consumer friendly language for the carton and the label for Alaway. The Agency's comments are stated in bold and Alimera's responses follow.

This response will be the basis for our scheduled teleconference on October 27, 2006.

If you have any questions or need additional information prior to October 27th, please contact me at 678-527-1330.

Sincerely,



Barbara H. Bauschka  
Manager, Regulatory Affairs

**NDA REGULATORY FILING REVIEW**  
**(Including Memo of Filing Meeting)**

NDA # 21-996

Supplement #

Efficacy Supplement Type SE-

Trade Name: —

Established Name: ketotifen fumarate ophthalmic solution

Strengths: 0.025%

Applicant: Alimera Sciences, Inc.

Agent for Applicant:

Date of Application: January 31, 2006

Date of Receipt: February 1, 2006

Date clock started after UN:

Date of Filing Meeting: March 17, 2006

Filing Date: March 18, 2006

Action Goal Date (optional):

User Fee Goal Date: 12-1-06

Indication(s) requested: \_\_\_\_\_

Type of Original NDA:

(b)(1)

(b)(2) X

OR

Type of Supplement:

(b)(1)

(b)(2)

**NOTE:**

(1) If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application is a (b)(2), complete Appendix B.

(2) If the application is a supplement to an NDA, please indicate whether the NDA is a (b)(1) or a (b)(2) application:

NDA is a (b)(1) application

OR

NDA is a (b)(2) application

Therapeutic Classification: S X

P

Resubmission after withdrawal?

Resubmission after refuse to file?

Chemical Classification: (1,2,3 etc.) 8

Other (orphan, OTC, etc.)

Form 3397 (User Fee Cover Sheet) submitted:

YES X NO

User Fee Status:

Paid

Exempt (orphan, government)

Waived (e.g., small business, public health) X

**NOTE:** If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx-to-OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the

Version: 12/15/2004

This is a locked document. If you need to add a comment where there is no field to do so, unlock the document using the following procedure. Click the 'View' tab; drag the cursor down to 'Toolbars'; click on 'Forms.' On the forms toolbar, click the lock/unlock icon (looks like a padlock). This will allow you to insert text outside the provided fields. The form must then be relocked to permit tabbing through the fields.

product described in the application. Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the user fee staff.

- Is there any 5-year or 3-year exclusivity on this active moiety in an approved (b)(1) or (b)(2) application? YES  NO X  
If yes, explain:

- Does another drug have orphan drug exclusivity for the same indication? YES  NO X

- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? YES  NO

If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES  NO X  
If yes, explain:

- If yes, has OC/DMPQ been notified of the submission? YES  NO

- Does the submission contain an accurate comprehensive index? YES X NO

- Was form 356h included with an authorized signature? YES X NO   
**If foreign applicant, both the applicant and the U.S. agent must sign.**

- Submission complete as required under 21 CFR 314.50? YES X NO   
If no, explain:

- If an electronic NDA, does it follow the Guidance? N/A X YES  NO   
**If an electronic NDA, all forms and certifications must be in paper and require a signature.**  
Which parts of the application were submitted in electronic format?

Additional comments:

- If an electronic NDA in Common Technical Document format, does it follow the CTD guidance? N/A X YES  NO

- Is it an electronic CTD (eCTD)? N/A  YES  NO X  
**If an electronic CTD, all forms and certifications must either be in paper and signed or be electronically signed.**

Additional comments:

- Patent information submitted on form FDA 3542a? YES X NO

- Exclusivity requested? YES, \_\_\_\_\_ Years NO X  
**NOTE: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.**

- Correctly worded Debarment Certification included with authorized signature? YES X NO   
**If foreign applicant, both the applicant and the U.S. Agent must sign the certification.**

*NOTE: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as "To the best of my knowledge . . . ."*

- Financial Disclosure forms included with authorized signature? YES X NO   
**(Forms 3454 and 3455 must be included and must be signed by the APPLICANT, not an agent.)**  
*NOTE: Financial disclosure is required for bioequivalence studies that are the basis for approval.*
- Field Copy Certification (that it is a true copy of the CMC technical section)? Y X NO
- PDUFA and Action Goal dates correct in COMIS? YES X NO   
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.
- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered.
- List referenced IND numbers: 69,164
- End-of-Phase 2 Meeting(s)? Date(s) \_\_\_\_\_ NO X  
If yes, distribute minutes before filing meeting.
- Pre-NDA Meeting(s)? Date(s) \_\_\_\_\_ NO X  
If yes, distribute minutes before filing meeting.

**Project Management**

- Was electronic "Content of Labeling" submitted? YES X NO  
If no, request in 74-day letter.
- All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC? YES X NO
- Risk Management Plan consulted to ODS/IO? N/A X YES  NO
- Trade name (plus PI and all labels and labeling) consulted to ODS/DMETS? Y X NO
- MedGuide and/or PPI (plus PI) consulted to ODS/DSRCS? N/A X YES  NO
- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted? N/A X YES  NO

**If Rx-to-OTC Switch application:**

- OTC label comprehension studies, all OTC labeling, and current approved PI consulted to ODS/DSRCS? N/A  YES X NO

- Has DOTCDP been notified of the OTC switch application? YES X NO

**Clinical**

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? N/A  
YES  NO

**Chemistry**

- Did applicant request categorical exclusion for environmental assessment? YES X NO   
If no, did applicant submit a complete environmental assessment? YES  NO   
If EA submitted, consulted to Florian Zielinski (HFD-357)? YES  NO
- Establishment Evaluation Request (EER) submitted to DMPQ? YES X NO
- If a parenteral product, consulted to Microbiology Team (HFD-805)? YES X NO

**APPEARS THIS WAY  
ON ORIGINAL**

ATTACHMENT

**MEMO OF FILING MEETING**

DATE: March 17, 2006

**BACKGROUND:** Alimera Sciences, Inc. (Alimera), has submitted a 505(b)(2) application for a RX to OTC switch for Ketotifen. The application is relying on the Agency's previous findings of safety and efficacy for Zaditor™ (ketotifen fumarate ophthalmic solution, 0.025%) marketed by Novartis Pharmaceuticals Corporation, NDA 21-066. Alimera is relying on the pre-clinical and clinical portions of NDA 21-066 for which Alimera does not have a right of reference. A bioequivalence study comparing Alimera's product to Zaditor demonstrated Alimera's product to be therapeutically equivalent to Zaditor.

**ATTENDEES:**

Division of Anti-Infective and Ophthalmology Products

Wiley Chambers, MD, Deputy Division Director  
Jennifer Harris, MD, Medical Officer  
Lucious Lim, MD, Medical Officer  
Rhea Lloyd, MD, Medical Officer  
Martin Nevitt, MD, Medical Officer  
Zhou Chen, PhD, Pharmacology Reviewer  
Terry Peters, DVM, Pharmacology Team Leader  
Lin Qi, PhD, Review Chemist  
Venkat Jarugula, PhD, Biopharm Team Leader  
Mike Puglisi, Project Manager  
Raphael Rodriguez, Project Manager  
Alison Rodgers, Project Manager

Division of Non-Prescription Clinical Evaluation

Keith Olin, Project Manager  
Steve Osborne, MD, Medical Officer  
Davia Shetty, MD, Medical Team Leader  
Michael Benson  
Marina Chang

**ASSIGNED REVIEWERS (including those not present at filing meeting) :**

<u>Discipline</u>	<u>Reviewer</u>
Medical:	Lucious Lim
Secondary Medical:	Steve Osborne
Statistical:	N/A
Pharmacology:	Zhou Chen
Statistical Pharmacology:	
Chemistry:	Lin Qi
Environmental Assessment (if needed):	
Biopharmaceutical:	N/A
Microbiology, sterility:	Bryan Riley
Microbiology, clinical (for antimicrobial products only):	N/A
DSI:	N/A
Regulatory Project Management:	Alison Rodgers/Keith Olin
Other Consults:	

Per reviewers, are all parts in English or English translation?  
If no, explain:

YES X NO

CLINICAL

FILE X

REFUSE TO FILE

- Clinical site inspection needed? YES  NO X
- Advisory Committee Meeting needed? YES, date if known \_\_\_\_\_ NO X
- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? N/A X YES  NO

CLINICAL MICROBIOLOGY

N/A

FILE

REFUSE TO FILE

STATISTICS

N/A X

FILE

REFUSE TO FILE

BIOPHARMACEUTICS

N/A

FILE

REFUSE TO FILE

- Biopharm. inspection needed? YES  NO

PHARMACOLOGY

N/A

FILE X

REFUSE TO FILE

- GLP inspection needed? YES  NO

CHEMISTRY

FILE X

REFUSE TO FILE

- Establishment(s) ready for inspection? YES  NO
- Microbiology YES X NO

**ELECTRONIC SUBMISSION:**

Any comments: N/A

**REGULATORY CONCLUSIONS/DEFICIENCIES:**

(Refer to 21 CFR 314.101(d) for filing requirements.)

- The application is unsuitable for filing. Explain why:
- X The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.
- No filing issues have been identified.
- X Filing issues to be communicated by Day 74. List (optional):

**ACTION ITEMS:**

- 1.  If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.

2.  If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
3.  Convey document filing issues/no filing issues to applicant by Day 74.

Alison Rodgers  
Regulatory Project Manager, HFD-520

**APPEARS THIS WAY  
ON ORIGINAL**

### Appendix A to NDA Regulatory Filing Review

An application is likely to be a 505(b)(2) application if:

- (1) it relies on literature to meet any of the approval requirements (unless the applicant has a written right of reference to the underlying data)
- (2) it relies on the Agency's previous approval of another sponsor's drug product (which may be evidenced by reference to publicly available FDA reviews, or labeling of another drug sponsor's drug product) to meet any of the approval requirements (unless the application includes a written right of reference to data in the other sponsor's NDA)
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)
- (4) it seeks approval for a change from a product described in an OTC monograph and relies on the monograph to establish the safety or effectiveness of one or more aspects of the drug product for which approval is sought (see 21 CFR 330.11).

Products that may be likely to be described in a 505(b)(2) application include combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations), OTC monograph deviations, new dosage forms, new indications, and new salts.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, please consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

**Appendix B to NDA Regulatory Filing Review  
Questions for 505(b)(2) Applications**

1. Does the application reference a listed drug (approved drug)? YES X NO

*If "No," skip to question 3.*

2. Name of listed drug(s) referenced by the applicant (if any) and NDA/ANDA #(s):Zaditor NDA 21-066

3. The purpose of this and the questions below (questions 3 to 5) is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval and that should be referenced as a listed drug in the pending application.

- (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved?

YES X NO

*(Pharmaceutical equivalents are drug products in identical dosage forms that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; and (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c))*

*If "No," skip to question 4. Otherwise, answer part (b).*

- (b) Is the approved pharmaceutical equivalent(s) cited as the listed drug(s)? YES X NO   
(The approved pharmaceutical equivalent(s) should be cited as the listed drug(s).)

*If "Yes," skip to question 6. Otherwise, answer part (c).*

- (c) Have you conferred with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007)? YES  NO

*If "No," please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.*

4. (a) Is there a pharmaceutical alternative(s) already approved? YES  NO

*(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)*

*If "No," skip to question 5. Otherwise, answer part (b).*

- (b) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)? YES  NO   
(The approved pharmaceutical alternative(s) should be cited as the listed drug(s).)

**NOTE:** *If there is more than one pharmaceutical alternative approved, consult the Director, Division of*

*Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007) to determine if the appropriate pharmaceutical alternatives are referenced.*

*If "Yes," skip to question 6. Otherwise, answer part (c).*

- (c) Have you conferred with the Director, Division of Regulatory Policy II, ORP? YES  NO

*If "No," please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.*

5. (a) Is there an approved drug product that does not meet the definition of "pharmaceutical equivalent" or "pharmaceutical alternative," as provided in questions 3(a) and 4(a), above, but that is otherwise very similar to the proposed product? YES  NO

*If "No," skip to question 6.*

*If "Yes," please describe how the approved drug product is similar to the proposed one and answer part (b) of this question. Please also contact the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007), to further discuss.*

- (b) Is the approved drug product cited as the listed drug? YES  NO
6. Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution"). Change from RX to OTC.
7. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA will refuse-to-file such NDAs (see 21 CFR 314.101(d)(9)).) YES  NO X
8. Is the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application should be refused for filing under 21 CFR 314.101(d)(9)). YES  NO X
9. Is the rate at which the product's active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD (see 21 CFR 314.54(b)(2))? If yes, the application should be refused for filing under 21 CFR 314.101(d)(9). YES  NO X
10. Are there certifications for each of the patents listed for the listed drug(s)? YES X NO
11. Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)
- 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)  
Patent number(s):
- 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)  
Patent number(s):

- 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)  
Patent number(s):
- X 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification)  
Patent number(s): 6774137, 6777429, 6776982

**NOTE:** IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must **subsequently** submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]. The applicant must also submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)].

- 21 CFR 314.50(i)(1)(ii): No relevant patents.
- 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)  
Patent number(s):
- 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).  
Patent number(s):
- Written statement from patent owner that it consents to an immediate effective date upon approval of the application.  
Patent number(s):

12. Did the applicant:

- Identify which parts of the application rely on information (e.g. literature, prior approval of another sponsor's application) that the applicant does not own or to which the applicant does not have a right of reference?  
YES X NO
- Submit a statement as to whether the listed drug(s) identified has received a period of marketing exclusivity?  
YES  NO X
- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug?  
N/A  YES X NO
- Certify that it is seeking approval only for a new indication and not for the indications approved for the listed drug if the listed drug has patent protection for the approved indications and the applicant is requesting only the new indication (21 CFR 314.54(a)(1)(iv).)?  
N/A X YES  NO

13. If the (b)(2) applicant is requesting 3-year exclusivity, did the applicant submit the following information required by 21 CFR 314.50(j)(4): N/A

- Certification that at least one of the investigations included meets the definition of "new clinical investigation" as set forth at 314.108(a). YES  NO

- A list of all published studies or publicly available reports that are relevant to the conditions for which the applicant is seeking approval. YES  NO

- EITHER

The number of the applicant's IND under which the studies essential to approval were conducted.

IND# \_\_\_\_\_ NO

OR

A certification that the NDA sponsor provided substantial support for the clinical investigation(s) essential to approval if it was not the sponsor of the IND under which those clinical studies were conducted?

YES  NO

14. Has the Associate Director for Regulatory Affairs, OND, been notified of the existence of the (b)(2) application?

YES X NO

**APPEARS THIS WAY  
ON ORIGINAL**

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

-----  
Alison Rodgers  
10/24/2006 03:55:44 PM  
CSO

**MEMORANDUM**

**DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH**

---

**CLINICAL INSPECTION SUMMARY**

DATE: October 24, 2006

TO: Allison Rodgers, Regulatory Project Manager  
William Boyd, M.D., Clinical Reviewer  
Division of Anti-inflammatory and Ophthalmic Products, HFD-550

THROUGH: Leslie K. Ball, M.D.  
Branch Chief  
Good Clinical Practice Branch 2, HFD-47  
Division of Scientific Investigations

FROM: Dianne Tesch, Consumer Safety Officer

SUBJECT: Evaluation of Clinical Inspections

NDA: 21-996

NME: No

APPLICANT: Alimera, Inc.

DRUG: ketotifen

THERAPEUTIC CLASSIFICATION: Standard Review

INDICATION: allergic conjunctivitis

CONSULTATION REQUEST DATE: June 21, 2006

DIVISION ACTION GOAL DATE: October 15, 2006

PDUFA DATE: December 1, 2006

**I. BACKGROUND:**

This is a new formulation of an approved drug, ketotifen fumarate, used to treat the symptoms of allergic conjunctivitis. This is a single center study. Dr. Torkildsen's site was the only one doing the study. There were no problems identified by the review division.

The investigational product is a new formulation of an approved product used to treat the symptoms of allergic conjunctivitis. The comparator was the original formulation of ketotifen fumarate 0.025%. The study took place during four visits over a five week period.

The primary efficacy endpoint was relief of ocular itching following conjunctival allergen challenge (CAC). The subjective mean ocular itching score assessed at 3, 5, and 7 minutes post CAC was used to determine primary efficacy. The secondary efficacy assessments, objective mean ocular redness and

chemosis scores, subjective mean lid swelling scores, and presence of tearing and mucus discharge, were assessed at 7, 15, and 20 minutes post CAC. Safety assessments included drop comfort, slit-lamp biomicroscopy, visual acuity (ETDRS), and adverse events.

Dr. Torkildsen has no prior inspectional history.

II. RESULTS (by protocol/site):

Name of CI and site #, if known	City, State*	Protocol #	Insp. Date	EIR Received Date	Final Classification
Gail Torkildsen	North Andover, MA	ASI-003	10/5-10/12/06	10/20/06	NAI

\*If international site, please insert column for country.

Key to Classifications

NAI = No deviation from regulations. Data acceptable.

VAI-No Response Requested= Deviations(s) from regulations. Data acceptable.

VAI-Response Requested = Deviation(s) from regulations. See specific comments below for data acceptability

OAI = Significant deviations for regulations. Data unreliable.

A. Protocol #ASI-003

1. Gail Torkildsen, M.D., North Andover, MA:

- a. One hundred seventy two subjects were screened, 108 were randomized, and 103 subjects completed the study. Thirty four records were reviewed in depth for the audit.
- b. There were no limitations to the inspection.
- c. There were no regulatory deficiencies..
- d. The data are acceptable for consideration in the NDA review decision.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

The study appears to have been well conducted. No follow up other than routine surveillance is indicated.

{See appended electronic signature page}

Dianne Tesch, Consumer Safety Officer

CONCURRENCE:

Supervisory comments

{See appended electronic signature page}

Leslie K. Ball, M.D.  
Branch Chief  
Good Clinical Practice Branch II  
Division of Scientific Investigations

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

/s/

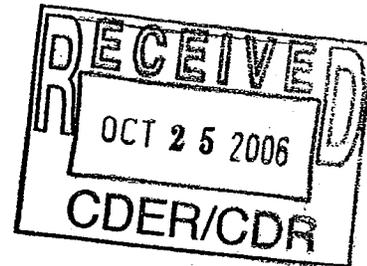
-----  
Dianne Tesch  
10/24/2006 12:04:59 PM  
CSO

Leslie Ball  
10/25/2006 03:43:04 PM  
MEDICAL OFFICER

**LIMERA**  
SCIENCES

*N-0005C*  
ORIG AMENDMENT

ORIGINAL



October 23, 2006

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Anti-Infective and Ophthalmology Products  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

RECEIVED

OCT 26 2006

CDER White Oak DR 1

**Re: NDA 21-996**  
**Ketotifen Fumarate Ophthalmic Solution, 0.025%**  
**Amendment: Response to CMC Comments - Request for Information**

Dear Sir or Madam:

Alimera Sciences, Inc. is providing our response to the CMC Comment of October 20, 2006. For ease of the review the Agency's comment is in bold and Alimera's response follows.

If you have any questions or need additional information please contact me at 678-527-1330.

Sincerely,

*Barbara H. Bauschka*

Barbara H. Bauschka  
Manager, Regulatory Affairs

Windward Parkway, Suite 290  
Doraville, GA 30005

Phone 678.990.5740 Fax 678.990.5744  
www.alimerasciences.com

**LIMERA**  
**SCIENCES**

ORIGINAL

**RECEIVED**

OCT 19 2006

**CDER CDR**

October 17, 2006

ORIGINAL AMENDMENT

N-000-BC **RECEIVED**

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Anti-Infective and Ophthalmology Products  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

OCT 20 2006

**CDER White Oak DR 1**

**Re: NDA 21-996**  
**Ketotifen Fumarate Ophthalmic Solution, 0.025%**  
**Amendment: Response to CMC Comments - Request for Information**

Dear Sir or Madam:

Alimera Sciences, Inc. is providing responses to the CMC Comments of September 26, 2006. For ease of the review the Agency's comments are in bold and Alimera's responses follow.

If you have any questions or need additional information please contact me at 678-527-1330.

Sincerely,

*Barbara H. Bauschka*

Barbara H. Bauschka  
Manager, Regulatory Affairs

Windward Parkway, Suite 290  
Atlanta, GA 30005

Phone 678.990.5740 Fax 678.990.5744  
www.alimerasciences.com

**ALIMERA**  
SCIENCES

**ORIGINAL**

RECEIVED  
OCT 16 2006  
CDR / CDER

October 12, 2006

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Anti-Infective and Ophthalmology Products  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

ORIGINAL AMENDMENT

*N(BL)*

RECEIVED

Re: **NDA 21-996**  
**Ketotifen Fumarate Ophthalmic Solution, 0.025%**  
**Amendment: Draft Labeling Response**

OCT 17 2006

CDER White Oak DR 1

Dear Sir or Madam:

Alimera Sciences, Inc. is providing responses to the email of October 5, 2006 with the Draft Labeling for the Drug Facts, carton and label for Alaway (ketotifen fumarate ophthalmic solution, 0.025%). The Agency's comments are stated in bold and Alimera's responses follow. The Drug Facts have a section-by-section response from Alimera.

This response will be the basis for our scheduled teleconference on October 17, 2006.

Additionally, no comments were received about the opposite side of the Drug Facts sheet which will be placed inside the carton. Alimera is including that page as part of the submission and would like to discuss during the teleconference.

If you have any questions or need additional information prior to October 17th, please contact me at 678-527-1330.

Sincerely,

*Barbara H. Bauschka*

Barbara H. Bauschka  
Manager, Regulatory Affairs

Windward Parkway, Suite 290  
Marietta, GA 30005

Phone 678.990.5740 Fax 678.990.5744  
www.alimerasciences.com

**ALIMERA**  
SCIENCES

**ORIGINAL**

October 20, 2006

**CDER/CDR**

**OCT 23 2006**

**RECEIVED**

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Anti-Infective and Ophthalmology Products  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

**RECEIVED**

**OCT 24 2006**

**CDER White Oak DR1**

**Re: NDA 21-996**  
**Ketotifen Fumarate Ophthalmic Solution, 0.025%**  
**-Amendment: Draft Labeling Response**

**ORIGINAL AMENDMENT**

*NCL*

Dear Sir or Madam:

Alimera Sciences, Inc. is providing further responses to the email of October 5, 2006 and results of the teleconference with the Agency on October 17, 2006 on the Draft Labeling for Alaway. This response includes the Drug Facts, carton and label for Alaway (ketotifen fumarate ophthalmic solution, 0.025%). The Agency's comments are stated in bold and Alimera's responses follow. The Drug Facts have a section-by-section response from Alimera and full copy.

This response will be the basis for our scheduled teleconference on October 27, 2006.

If you have any questions or need additional information prior to October 27th, please contact me at 678-527-1330.

Sincerely,

*Barbara H. Bauschka*

Barbara H. Bauschka  
Manager, Regulatory Affairs



September 20, 2006

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Anti-Infective and Ophthalmology Products  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

Re: **NDA 21-996**  
**Ketotifen Fumarate Ophthalmic Solution, 0.025%**  
**Amendment: Response to CMC Comments - Request for Information**

Dear Sir or Madam:

Alimera Sciences, Inc. is providing responses to the CMC Comments of September 18, 2006 and the telephone conversation with the Agency of September 20, 2006. For ease of the review the Agency's comments are in bold and Alimera's responses follow. Additionally, as requested, the responses will be sent via facsimile to the reviewer, Lin Qi, Ph.D.

If you have any questions or need additional information please contact me at 678-527-1330.

Sincerely,

A handwritten signature in cursive script that reads "Barbara H. Bauschka".

Barbara H. Bauschka  
Manager, Regulatory Affairs

Cc: Lin Qi, Ph.D., via facsimile

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0338  
Expiration Date: September 30, 2008  
See OMB Statement on page 2.

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC,  
OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT Alimera Sciences, Inc.	DATE OF SUBMISSION 09/20/2006
TELEPHONE NO. (Include Area Code) 678-527-1330	FACSIMILE (FAX) Number (Include Area Code) 678-990-5743
APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued): 6120 Windward Parkway, Suite 290 Alpharetta GA 30005	AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued)	21-996	
ESTABLISHED NAME (e.g., Proper name, USP/USAN name) ketotifen fumarate ophthalmic solution, 0.025%	PROPRIETARY NAME (trade name) IF ANY	
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (If any)	CODE NAME (If any)	
DOSAGE FORM: ophthalmic solution	STRENGTHS: 0.025%	ROUTE OF ADMINISTRATION: ophthalmic topical
(PROPOSED) INDICATION(S) FOR USE: [ ]		

APPLICATION INFORMATION

APPLICATION TYPE (check one) <input checked="" type="checkbox"/> NEW DRUG APPLICATION (NDA, 21 CFR 314.50) <input type="checkbox"/> ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94) <input type="checkbox"/> BIOLOGICS LICENSE APPLICATION (BLA, 21 CFR Part 601)
IF AN NDA, IDENTIFY THE APPROPRIATE TYPE <input type="checkbox"/> 505 (b)(1) <input checked="" type="checkbox"/> 505 (b)(2)
IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION Name of Drug: Zaditor Holder of Approved Application: Novartis Pharmaceuticals, Inc.
TYPE OF SUBMISSION (check one) <input type="checkbox"/> ORIGINAL APPLICATION <input checked="" type="checkbox"/> AMENDMENT TO A PENDING APPLICATION <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> PRESUBMISSION <input type="checkbox"/> ANNUAL REPORT <input type="checkbox"/> ESTABLISHMENT DESCRIPTION SUPPLEMENT <input type="checkbox"/> EFFICACY SUPPLEMENT <input type="checkbox"/> LABELING SUPPLEMENT <input type="checkbox"/> CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT <input type="checkbox"/> OTHER
IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION:
IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY <input type="checkbox"/> CBE <input type="checkbox"/> CBE-30 <input type="checkbox"/> Prior Approval (PA)
REASON FOR SUBMISSION
PROPOSED MARKETING STATUS (check one) <input type="checkbox"/> PRESCRIPTION PRODUCT (Rx) <input checked="" type="checkbox"/> OVER THE COUNTER PRODUCT (OTC)
NUMBER OF VOLUMES SUBMITTED: 01 THIS APPLICATION IS <input checked="" type="checkbox"/> PAPER <input type="checkbox"/> PAPER AND ELECTRONIC <input type="checkbox"/> ELECTRONIC
ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the application.) Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready. [ ]

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

[ ]
-----

This application contains the following items: (Check all that apply)

<input type="checkbox"/>	1. Index
<input type="checkbox"/>	2. Labeling (check one) <input type="checkbox"/> Draft Labeling <input type="checkbox"/> Final Printed Labeling
<input type="checkbox"/>	3. Summary (21 CFR 314.50 (c))
<input type="checkbox"/>	4. Chemistry section
<input type="checkbox"/>	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
<input type="checkbox"/>	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
<input type="checkbox"/>	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
<input type="checkbox"/>	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
<input type="checkbox"/>	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
<input type="checkbox"/>	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
<input type="checkbox"/>	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
<input type="checkbox"/>	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
<input type="checkbox"/>	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
<input type="checkbox"/>	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
<input type="checkbox"/>	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
<input type="checkbox"/>	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
<input type="checkbox"/>	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
<input type="checkbox"/>	15. Establishment description (21 CFR Part 600, if applicable)
<input type="checkbox"/>	16. Debarment certification (FD&C Act 306 (k)(1))
<input type="checkbox"/>	17. Field copy certification (21 CFR 314.50 (l)(3))
<input type="checkbox"/>	18. User Fee Cover Sheet (Form FDA 3397)
<input type="checkbox"/>	19. Financial Information (21 CFR Part 54)
<input checked="" type="checkbox"/>	20. OTHER (Specify) <input type="checkbox"/> Response to Request for Information

**CERTIFICATION**

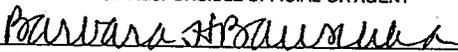
I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT		TYPED NAME AND TITLE	DATE
		Barbara H. Bauschka, Manager Regulatory Affairs	09/20/2006
ADDRESS (Street, City, State, and ZIP Code)		Telephone Number	
6120 Windward Parkway, Suite 290 Alpharetta GA 30005		678-527-1330	

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services  
 Food and Drug Administration  
 Center for Drug Evaluation and Research  
 Central Document Room  
 5901-B Ammendale Road  
 Beltsville, MD 20705-1266

Department of Health and Human Services  
 Food and Drug Administration  
 Center for Biologics Evaluation and Research (HFM-99)  
 1401 Rockville Pike  
 Rockville, MD 20852-1448

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

CMC Comments

1. It is recommended that the acceptance criterion for "Any individual unspecified impurity" remain as in the original specification as "Not more than — for impurities outside the scope of Q3B —"

Alimera Sciences, Inc. commits to a release and regulatory specification for "Individual Unspecified Impurities" of — as shown in the attached specification table.

2. It is recommended that the acceptance criterion for "Total (Specified and Unspecified) degradants" be tightened to "Not more than —"

Alimera Sciences, Inc. commits to revising the release and regulatory specification for "Total (Specified and Unspecified) Degradants to — as shown in the attached specification table.

3. Note that the Q3B (R2) model provides for an individual specification for any degradants above the identification threshold, whether identified or unidentified. The specification should also list, as stated in Q3B (R2), "Any unspecified degradation product with an acceptance criterion of not more than ( $\leq$ ) the identification threshold". Please revise your specification accordingly.

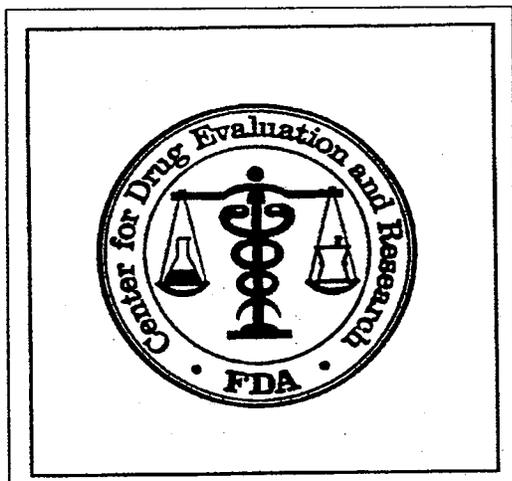
Alimera Sciences commits to revising the release and regulatory specifications for Individual Specified Identified Degradation Products and Individual Specified Unidentified Degradation Products as shown in the attached specification table and discussed in the telephone conversation with Dr. Qi of the Agency on September 20, 2006.

**APPEARS THIS WAY  
ON ORIGINAL**

Test	Release Specifications	Regulatory Specifications
✓		

**APPEARS THIS WAY  
ON ORIGINAL**

FACSIMILE TRANSMISSION  
RECORD



From: Lin Qi, Ph.D.

Office of New Drug Quality Assessment

Phone 301-796-1438

Fax 301-796-9850

Date: 9/25/06

To: Name Ms. Barbara H. Bauschka  
Company Alimera Sciences, Inc.  
City Alpharetta State GA  
Phone # 678-527-1330  
FAX # 678-990-5743

Number of Pages (INCLUDING COVER PAGE) 2

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**NDA 21-996**

**— (ketotifen fumarate ophthalmic solution) 0.025%**

These comments are being provided to you prior to completion of our review of the application to give you preliminary notice of issues that have been identified. Per the user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and are subject to change as the review of your application is finalized. In addition, we may identify other information that must be provided prior to approval of this application. Depending on the timing of your response, as per user fee reauthorization agreements, we may or may not be able to consider your response prior to taking an action on your application during this review cycle.

If your response can be found in the contents of your submission, just cite those sections of the submission that are relevant to the issue under consideration. Otherwise, provide the appropriate information. Your response should be submitted as an amendment to the submission and a copy via facsimile to the reviewer.

**CMC COMMENTS**

1. Please clarify if all coded impurities — listed in the drug product specification (amendment dated September 20, 2006) are degradation products based on your original degradation product study (in the original submission) and the updated stability data (amendments dated May25, 2006 and September 1, 2006). Clarify if structures of impurity — have been identified. Note that impurities present in a new drug substance need not be monitored or specified in new drug product unless they are also degradation products.
2. The analytical procedure, "HPLC Assay for the Analysis of Ketotifen Fumarate Impurities in Alimera Ketotifen Fumarate Ophthalmic Solution 0.025%", should be revised to specify the coded degradation products using relative retention time.
3. The analytical procedure, "HPLC Assay for the Analysis of Ketotifen Fumarate Impurities in Alimera Ketotifen Fumarate Ophthalmic Solution 0.025%", should be validated accordingly when it is used as a quantitative testing method for the impurity levels (reference to ICH Q2A).
4. Based on the available stability data, an appropriate shelf-life for Ketotifen Fumarate Ophthalmic Solution 0.025% is — months. Please revise your shelf-life proposal accordingly.

OTC Drug Labeling Review for Alaway™ (Ketotifen Fumarate)  
Ophthalmic Solution, 0.0345%

Office of Nonprescription Products  
Center for Drug Evaluation and Research • Food and Drug Administration

**NDA 21-996**

**SUBMISSION DATES:** January 31, 2006  
March 30, 2006  
June 28, 2006  
August 17, 2006

**REVIEW DATE:** September 19, 2006

**NDA (SUBMISSION TYPE)** NDA 21-996

**SPONSOR CONTACT:** Alimera Sciences  
Barbara H. Bauschka  
Manager, Regulatory Affairs  
1-678-527-1330

**DRUG PRODUCT:** Alaway™ Ophthalmic Solution, 0.025%

**ACTIVE INGREDIENT:** Ketotifen fumarate 0.0345% (equivalent to  
ketotifen 0.025%)

**INDICATIONS:** Temporarily relieves itchy eyes due to  
allergies caused by ragweed, pollen, grass,  
animal hair and dander.

**PHARMACOLOGIC CATEGORY:** Antihistamine

**LABELING SUBMITTED:** 1/31/06 - Carton and container label for 10  
mL SKU and Consumer information leaflet  
3/30/06 - Font specifications for Drug Facts  
labeling.  
6/28/06 - Name change from — to  
Alaway™ with new labeling  
8/17/06 - Revised carton labeling

**RECOMMENDATIONS:** Strikethrough for deletions.  
Red highlight for additions.

**BACKGROUND:**

Ketotifen fumarate 0.0345% (equivalent to ketotifen 0.025%) Ophthalmic Solution by Novartis was approved as a prescription drug product under NDA 21-066 on July 2, 1999. Alimera is proposing an Rx-to-OTC switch submitted under a 505(b)(2) application.



4 Page(s) Withheld

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

X § 552(b)(4) Draft Labeling

\_\_\_\_\_ § 552(b)(5) Deliberative Process

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/s/

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Michael Benson  
9/21/2006 01:47:38 PM  
INTERDISCIPLINARY

Marina Chang  
9/22/2006 07:52:12 AM  
INTERDISCIPLINARY

## MEMORANDUM OF TELECON

DATE: September 20, 2006

APPLICATION NUMBER: NDA 21-996

BETWEEN:

Name: Barbara Bauschka  
Susan Caballa  
Phone: 678-527-1330  
Representing: Alimera Sciences, Inc.

AND

Name: Lin Qi, PhD, Office of New Drug Quality Assessment  
Alison Rodgers, Division of Anti-Infective and Ophthalmology Products

SUBJECT: NDA 21-996

The CMC comments listed below were conveyed to Alimera Sciences, Inc. (Alimera), via email on September 18, 2006. Alimera requested clarification of the comments.

The comments are restated below in bold. The comments are followed by bulleted teleconference discussion points.

**The following comments pertain to the impurities listed in the drug product specification:**

- 1. It is recommended that the acceptance criterion for "Any individual unspecified impurity" remain as in the original specification as "Not more than \_\_\_\_\_" for impurities outside the scope of Q3B such as \_\_\_\_\_**
- 2. It is recommended that the acceptance criterion for "Total (Specified and Unspecified) degradants" be tightened to "Not more than \_\_\_\_\_"**
- 3. Note that the Q3B (R2) model provides for an individual specification for any degradant above the identification threshold, whether identified or unidentified. The specification should also list, as stated in Q3B (R2), "Any unspecified degradation product with an acceptance criterion of not more than ( $\leq$ ) the identification threshold". Please revise your specification accordingly.**

**Discussion Points:**

- The FDA noted that it would be acceptable for Alimera to list the unidentified degradants with levels above \_\_\_\_\_ and assign them acceptance criteria.

- Alimera agreed to tighten the acceptance criterion for “Total (Specified and Unspecified) degradants” to “not more than \_\_\_\_\_”.
- The FDA confirmed that any individual unspecified impurity should be no greater than \_\_\_\_\_.
- The FDA noted that relative retention time (RRT) \_\_\_\_\_ is sometimes \_\_\_\_\_ based on instruments used, so either A,B,C,D or RRT may be used; A,B,C,D is clearer.

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Alison Rodgers  
Project Manager

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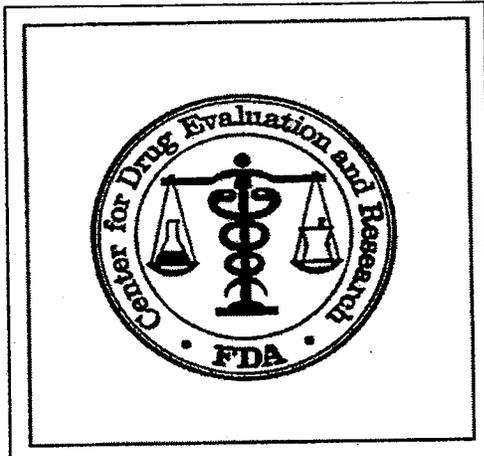
/s/

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Alison Rodgers  
9/20/2006 03:50:28 PM  
CSO

Alison Rodgers  
9/20/2006 03:57:06 PM  
CSO

Lin Qi  
9/20/2006 03:59:33 PM  
CHEMIST

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RECORD



From: Lin Qi, Ph.D.

Office of New Drug Quality Assessment

Phone 301-796-1438

Fax 301-796-9850

Date: 9/18/06

To: Name Ms. Barbara H. Bauschka  
Company Alimera Sciences, Inc.  
City Alpharetta State GA  
Phone # 678-527-1330  
FAX # 678-990-5743

Number of Pages (INCLUDING COVER PAGE) 2

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NDA 21-996

ketotifen fumarate ophthalmic solution) 0.025%

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If your response can be found in the contents of your submission, just cite those sections of the submission that are relevant to the issue under consideration. Otherwise, provide the appropriate information. Your response should be submitted as an amendment to the submission and a copy via facsimile to the reviewer.

### CMC COMMENTS

The following comments pertain to the impurities listed in the drug product specification:

1. It is recommended that the acceptance criterion for "Any individual unspecified impurity" remain as in the original specification as "Not more than —" for impurities outside the scope of Q3B such as —
2. It is recommended that the acceptance criterion for "Total (Specified and Unspecified) degradants" be tightened to "Not more than —".
3. Note that the Q3B (R2) model provides for an individual specification for any degradant above the identification threshold, whether identified or unidentified. The specification should also list, as stated in Q3B (R2), "Any unspecified degradation product with an acceptance criterion of not more than ( $\leq$ ) the identification threshold". Please revise your specification accordingly.

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/s/

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Alison Rodgers  
9/18/2006 03:23:12 PM

**ALIMERA**  
SCIENCES

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SEP 11 2006

CDER White Oak DR 1

**RECEIVED**

SEP 08 2006

CDER CDR

September 6, 2006

N-000 (B10)  
ORIG AMENDMENT

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Anti-Infective and Ophthalmology Products  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

**Re: NDA 21-996**  
**Ketotifen Fumarate Ophthalmic Solution, 0.025%**  
**Amendment: Response to Request for Information**

Dear Sir or Madam:

Alimera Sciences, Inc. is providing responses to the August 30, 2006 telephone request of Ms. Dianne Tesch of the Scientific Investigations area. For ease of the review the Agency's requests are in bold and Alimera's responses follow. Additionally, a desk copy is being forwarded to Ms. Tesch.

If you have any questions or need additional information please contact me at 678-527-1330.

Sincerely,

*Barbara H. Bauschka*

Barbara H. Bauschka  
Manager, Regulatory Affairs

Desk Copy: Ms. Dianne Tesch

Windward Parkway, Suite 290  
Rosetta, GA 30005

Phone 678.990.5740 Fax 678.990.5744  
www.alimerasciences.com

**MERA**  
NCES

ORIGINAL

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SEP 06 2006

CDER White Oak DR 1

RECEIVED

SEP 06 2006

CDER CDR

September 1, 2006

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Anti-Infective and Ophthalmology Products  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

ORIG AMENDMENT  
N-000-(BC)

**Re: NDA 21-996**  
**Ketotifen Fumarate Ophthalmic Solution, 0.025%**  
**Amendment: Response to CMC Comments - Request for Information**

Dear Sir or Madam:

Alimera Sciences, Inc. is providing responses to the CMC Comments of August 28, 2006. For ease of the review the Agency's comments are in bold and Alimera's responses follow. Additionally, as requested, the responses will be sent via facsimile to the reviewer, Lin Qi, Ph.D.

If you have any questions or need additional information please contact me at 678-527-1330.

Sincerely,

*Barbara H Bauschka*

Barbara H. Bauschka  
Manager, Regulatory Affairs

Cc: Lin Qi, Ph.D., via facsimile

**MERA**  
SCIENTIFIC  
SOLUTIONS

**ORIGINAL**

N-000-31

ORIG AMENDMENT

**RECEIVED**

SEP 0<sup>6</sup> 2006

**CDER/CDR**

August 30, 2006

**CDER White Oak DR1**

AUG 30 2006

**RECEIVED**

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Anti-Infective and Ophthalmology Products  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

**Re: NDA 21-996**  
**Ketotifen Fumarate Ophthalmic Solution, 0.025%**  
**Amendment: Response to Microbiology Review Request for Information**

Dear Sir or Madam:

Alimera Sciences, Inc. is providing the Microbial Retention Validation Study Protocol and Microbial Retention Validation Study Report for the \_\_\_\_\_ used with the drug product Ketotifen Fumarate Ophthalmic Solution, 0.025% as requested.

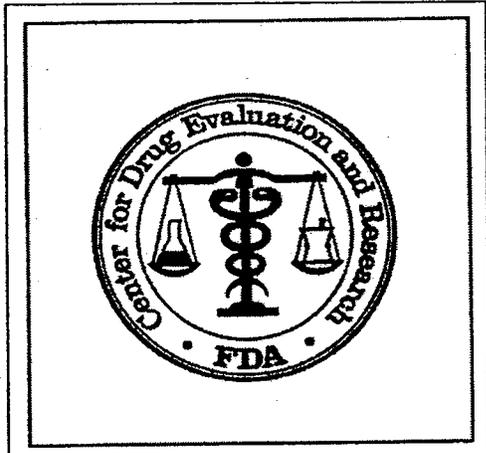
If you have any questions or need additional information please contact me at 678-527-1330.

Sincerely,

*Barbara H. Bauschka*

Barbara H. Bauschka  
Manager, Regulatory Affairs

FACSIMILE TRANSMISSION  
RECORD



From: Lin Qi, Ph.D.

Office of New Drug Quality Assessment

Phone 301-796-1438

Fax 301-796-9850

Date: 8/28/06

To: Name Ms. Barbara H. Bauschka  
Company Alimera Sciences, Inc.  
City Alpharetta State GA  
Phone # 678-527-1330  
FAX # 678-990-5743

Number of Pages (INCLUDING COVER PAGE) 2

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NDA 21-996

— (ketotifen fumarate ophthalmic solution) 0.025%

These comments are being provided to you prior to completion of our review of the application to give you preliminary notice of issues that have been identified. Per the user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and are subject to change as the review of your application is finalized. In addition, we may identify other information that must be provided prior to approval of this application. Depending on the timing of your response, as per user fee reauthorization agreements, we may or may not be able to consider your response prior to taking an action on your application during this review cycle.

If your response can be found in the contents of your submission, just cite those sections of the submission that are relevant to the issue under consideration. Otherwise, provide the appropriate information. Your response should be submitted as an amendment to the submission and a copy via facsimile to the reviewer.

### CMC COMMENTS

1. Please submit the Biological Reactivity Testing Results mentioned in Section 3.2.P.2.4.
2. Regarding the drug product specification:
  - a. Provide revised specification which includes the two ID tests as agreed in the submission of May 25, 2006.
  - b. Based on impurity levels reported in the submission of May 25, 2006, do you plan to revise the drug product specification?
3. \_\_\_\_\_  
\_\_\_\_\_ Please provide updated long term stability data to support the proposed shelf life.

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/s/

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Lin Qi  
8/28/2006 03:07:59 PM  
CHEMIST

Norman Schmuff  
8/29/2006 10:50:29 AM  
CHEMIST

## Rodgers, Alison

---

**From:** Rodgers, Alison  
**Sent:** Monday, August 28, 2006 10:07 AM  
**To:** 'Barbara Bauschka'  
**Subject:** NDA 21-996 - Information Request - Micro

**Importance:** High

Hi Barbara,

Please note below the information request from our Micro reviewer. Please let me know how soon you can respond.

The applicant should provide a summary of the results of a microbial retention study using the drug product and the proposed sterilizing — material (\_\_\_\_\_)

Thanks,

Alison

Alison K. Rodgers  
Regulatory Health Project Manager  
FDA/CDER  
Division of Anti-Infective and Ophthalmology Products  
Phone: 301-796-0797  
Fax: 301-796-9882  
Email: [alison.rodgers@fda.hhs.gov](mailto:alison.rodgers@fda.hhs.gov)

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/s/

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Alison Rodgers  
8/28/2006 10:19:18 AM  
CSO

Alison Rodgers  
8/28/2006 10:19:42 AM  
CSO

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AUG 21 2006  
CDER/CDR

August 18, 2006

N-090 (BL)  
ORIG AMENDMENT

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Anti-Infective and Ophthalmology Products  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

RECEIVED

AUG 22 2006

Re: **NDA 21-996**  
**Ketotifen Fumarate Ophthalmic Solution, 0.025%**  
**Amendment: Labeling**

CDER White Oak DR 1

Dear Sir or Madam:

Alimera Sciences, Inc. is submitting this amended labeling for **NDA 21-996** (Ketotifen Fumarate Ophthalmic Solution 0.025%) as the original proposed carton layout was altered for mechanical reasons. This amended labeling is only for the carton layout; no changes have been made to the label or the package information insert previously submitted June 28, 2006.

A desk copy is also being submitted to the Project Manager, Alison Rodgers. If you need additional information or have further questions, please contact me at 678-527-1330, fax 678-527-1335 or by email.

Sincerely,

*Barbara H Bauschka*

Barbara H. Bauschka  
Manager, Regulatory Affairs  
barbara.bauschka@alimerasciences.com

Desk Copy: Alison Rodgers, Project Manager

CDER/CDR

JUN 30 2006

RECEIVED

N-996 (EL)  
ORIG AMENDME.

June 28, 2006

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Anti-Infective and Ophthalmology Products  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

RECEIVED

JUL - 3 2006

Re: **NDA 21-996**  
**Ketotifen Fumarate Ophthalmic Solution, 0.025%**  
**Amendment: Labeling**

CDER White Oak DR 1

Dear Sir or Madam:

Alimera Sciences, Inc. is providing amended, annotated labeling for **NDA 21-996** (Ketotifen Fumarate Ophthalmic Solution 0.025%) as the original proposed name has been denied. This amended labeling uses one of the proposed names, Alaway, although the previous submission of May 24, 2006 also proposed the name — For the ease of the reviewer, there is an annotated copy of the labeling, as well as a full-color version.

A desk copy is also being submitted to the Project Manager, Alison Rodgers. If you need additional information or have further questions, please contact me at 678-527-1330, fax 678-527-1335 or by email.

Sincerely,

*Barbara H. Bauschka*

Barbara H. Bauschka  
Manager, Regulatory Affairs  
barbara.bauschka@alimerasciences.com

Desk Copy: Alison Rodgers, Project Manager

# ALIMERA SCIENCES

June 2, 2006

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Anti-Infective and Ophthalmology Products  
5901-B Ammendale Road  
Beltsville, MD, 20705-1266

**Re: NDA 21-996**  
**Ketotifen Fumarate Ophthalmic Solution, 0.025%**  
**General Correspondence: Carton Mock-up**

Dear Sir or Madam:

As requested by the Agency in an email May 31, 2006, Alimera Sciences, Inc. is submitting a mock-up of the proposed carton to be used for the drug product described in **NDA 21-996 Ketotifen Fumarate Ophthalmic Solution, 0.025%**.

The name on the carton — was the proposed name, which Alimera has since been advised will not be acceptable. As Alimera is awaiting notification of the use of possible alternatives, additional artwork for the carton has not been completed and — still appears on the mock-up carton.

Once Alimera receives notification that an alternate name is not already being used, graphics and associated artwork will commence. If additional information is required or there are questions about this request, please contact me at 678-527-1330, by fax at 678-527-1335 or by email.

Sincerely,



Barbara H. Bauschka  
Manager, Regulatory Affairs  
barbara.bauschka@alimerasciences.com

Cc: Alison Rodgers, Project Manager