

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21-996**

**CHEMISTRY REVIEW(S)**



**NDA 21-996**

**Alaway (Ketotifen Fumarate Ophthalmic Solution) 0.025%**

**Alimera**

**Lin Qi, Ph.D.**

**Division of Anti-infective and Ophthalmic Drug Products**

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**Chemistry Review Data Sheet**

- 1. NDA 21-996
- 2. REVIEW #: 1
- 3. REVIEW DATE: October 27, 2006
- 4. REVIEWER: Lin Qi
- 5. PREVIOUS DOCUMENTS:

Previous Documents

Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Document Date

Original

Jan 31, 2006

Amendment

May 25, 2006

Amendment

Sept 1, 2006

Amendment

Sept 20, 2006

Amendment

Oct 17, 2006

Amendment

Oct 23, 2006

7. NAME & ADDRESS OF APPLICANT:

Name: Alimera Sciences, Inc.  
Address: 6120 Windward Parkway, Suite 290  
Alpharetta GA 30005  
Representative: Barbara H. Bauschka  
Telephone: 678-527-1330

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Alaway
- b) Non-Proprietary Name (USAN): Ketotifen Fumarate Ophthalmic Solution 0.025%

## Chemistry Review Data Sheet

c) Code Name/# (ONDC only):

d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

10. PHARMACOL. CATEGORY: Antihistamine

11. DOSAGE FORM: Solution

12. STRENGTH/POTENCY: 0.025% (Ketotifen)

13. ROUTE OF ADMINISTRATION: Ophthalmic

14. Rx/OTC DISPENSED:  Rx  OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

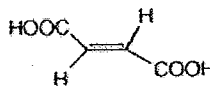
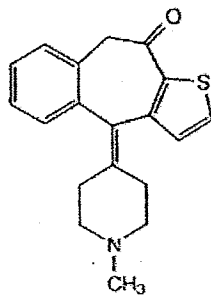
SPOTS product – Form Completed

Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name: 4-(1-Methyl-piperidylidene)-4H-benzo-[4,5]-cyclohepta-[1,2-b]-thiophene-10(9H)-one hydrogen fumarate anhydrous

Structural Formula:



Chemistry Review Data Sheet

Molecular Formula: C<sub>19</sub>H<sub>19</sub>NOS·C<sub>4</sub>H<sub>4</sub>O<sub>4</sub>

**17. RELATED/SUPPORTING DOCUMENTS:**

**A. DMFs:**

DMF #	TYP E	HOLDER	ITEM REFERENCED	CODE <sub>1</sub>	STATUS <sub>2</sub>	DATE REVIEW COMPLETED	COMMENTS
				3	Adequate	July 5, 2005	
				7			To be reviewed by a microbiologist
				3	Adequate	Jan 14, 2005	
				4			
				4			
				4			

<sup>1</sup> Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

<sup>2</sup> Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

**B. Other Documents:**

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	21-066	Zaditor (Ketotifen Fumarate Ophthalmic Solution) EQ 0.025% base, Novartis
ANDA	77-354	Ketotifen Fumarate Ophthalmic Solution EQ 0.025% base, Apotex Inc.

Chemistry Review Data Sheet

18. STATUS:

**ONDC:**

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics			
EES	Acceptable	3/17/2006	S. FERGUSON
Pharm/Tox			
Biopharm			
LNC			
Methods Validation	Found acceptable in this review	10/25/06	Lin Qi
OPDRA			
EA			
Microbiology			

**OGD:**

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology			
EES			
Methods Validation			
Labeling			
Bioequivalence			
EA			
Radiopharmaceutical			

19. ORDER OF REVIEW (OGD Only)

The application submission(s) covered by this review was taken in the date order of receipt.  Yes  No If no, explain reason(s) below:



**The Chemistry Review for NDA 21-996**

**The Executive Summary**

**I. Recommendations**

**A. Recommendation and Conclusion on Approvability**

This NDA is recommended for approval based on the quality assessment.

**B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable**

None.

**II. Summary of Chemistry Assessments**

**A. Description of the Drug Product(s) and Drug Substance(s)**

The drug product, Ketotifen Ophthalmic Solution 0.025%, is a sterile, preserved multi-dose ophthalmic solution intended for temporary relief of itchy eyes due to ragweed, pollen, grass, animal hair and dander. The current formulation, \_\_\_\_\_

\_\_\_\_\_ The drug product should be stored at 4 - 25°C (39 - 77°F).

The drug substance, ketotifen fumarate, is a white to light yellow, odorless, crystalline powder. It is slightly soluble in methanol, sparingly soluble in water, very slightly soluble in ethyl acetate, chloroform and acetonitrile. Its melting point is between 192°C and 195°C with decomposition. There is no polymorphic form observed by differential scanning calorimetric examination. The drug substance acceptance specification is based on the Ph. Eur.



**B. Description of How the Drug Product is Intended to be Used**

The drug product, Ketotifen Ophthalmic Solution 0.025%, is applied as an Over-the-Counter antihistamine drug. It is indicated for the temporary relief of itchy eyes due to ragweed, pollen, grass, animal hair and dander. The dosage for adults and children 3 years and older is 1 drop in the affected eye (s) twice daily.

**C. Basis for Approvability or Not-Approval Recommendation**

The drug substance section was submitted in DMF — and found acceptable by Dr. Liang-Lit Huang in his review #3 dated July 15, 2005.

The drug product section was evaluated in this review. During the review process, issues regarding the impurity analysis procedure, method validation, and lack of stability data to support the proposed shelf life were communicated with the applicant. The applicant provided revised impurity analysis procedure, complete impurity profile, and updated stability data. Therefore, the proposed shelf life of 24 months is justified. The drug product specification was revised with updated stability data. There is no unsolved quality issue for this application.

**III. Administrative****A. Reviewer's Signature**

See electronic signatures in DFS.

**B. Endorsement Block**

ChemistName/Date: Lin Qi  
BranchChiefName/Date: Norman Schmuft  
ProjectManagerName/Date: Alison Rodgers

73 Page(s) Withheld

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

       § 552(b)(4) Draft Labeling

       § 552(b)(5) Deliberative Process

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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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Lin Qi  
11/6/2006 06:27:17 PM  
CHEMIST

Norman Schmuff  
11/7/2006 07:12:00 AM  
CHEMIST