CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-996

PHARMACOLOGY REVIEW(S)

Memorandum for NDA 21-996
Submission Date: January 31, 2006

To:	**Alison Rodgers**
From:	**Zhou Chen, PhD**
Through:	**Terry Peters, DVM**
Date:	**March 15, 2006**
Re:	**NDA 21-996** **Application for the switch of prescription (Rx) to OTC** **Alimera Sciences, Inc.**

Ketotifen is a selective, non-competitive antagonist of the histamine (H_1) receptor. Ketotifen fumarate ophthalmic solution 0.025% (Zaditor™) was approved in the United States in 1999 for the temporary prevention of itching of the eye due to allergic conjunctivitis.

In January 2006, the sponsor submitted a NDA with a new formulation of ketotifen fumarate, requesting FDA's input on their plan to switch prescription ketotifen fumarate to OTC. The new formulation and the marketed formulation are listed in the table below.

Component: standard quantity per ml (mg)	Standard quantity per ml (mg)	Marketed formulation	Function
Ketotifen fumarate	0.345 (equivalent to 0.25 mg ketotifen)	0.345	Active
Glycerin USP			
Benzalkonium chloride NF			
Sodium hydroxide, NF			
Hydrochloride acid, NF			
Water for injection, USP			

The sponsor indicated that since this is a 505(b)(2) application, they have no new relevant information for nonclinical study sections in this NDA.

A battery of toxicology studies, including one-year systemic toxicity studies in monkeys and dogs, 3-month systemic toxicity study in rats, and 6-month ocular toxicity study in rabbits, were conducted under NDA 21-066. No toxicologically significant findings were noted.

Glycerin has been used in approved ophthalmic drugs with the concentrations of up to 3%. The sponsor has performed a clinical bioequivalence study demonstrating that the new formulation is "therapeutically equivalent to Zaditor™." Glycerin has been used in many drugs with different administration routes including oral, intravenous, topical ocular, or rectal route with the maximum daily dose of 120 g, much higher than the doses (up to 18 mg/day) proposed for this drug. It appears that systemic toxicity for glycerin is not a concern. Regarding local tolerance, if the drug with the new formulation was well-tolerated in the finished clinical study, no nonclinical studies are necessary.

There are no outstanding pharmacology/toxicology issues for ketotifen fumarate. Ketotifen has been shown to have little systemic exposure following topical ocular administration. Oral ketotifen has been approved in Japan, Canada and European countries for the treatment of asthma. Ophthalmic ketotifen fumarate 0.05% was investigated in Japan and was judged as

effective, safe and well tolerated. The drug has been marketed in Japan since 1991. In conclusion, this NDA is fileable.

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/s/

Zhou Chen
3/15/2006 04:10:13 PM
PHARMACOLOGIST

Terry Peters
3/17/2006 12:53:44 PM
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Memorandum for NDA 21-996
Submission Date: January 31, 2006

To:	**Alison Rodgers**
From:	**Zhou Chen, MD, PhD**
Through:	**Terry Peters, DVM**
Date:	**May 18, 2006**
Re:	**NDA 21-996** **New formulation of ketotifen fumarate ophthalmic solution 0.025%** **Alimera Sciences, Inc.**

Ketotifen is a selective, non-competitive antagonist of the histamine (H_1) receptor. Ketotifen fumarate ophthalmic solution 0.025% (Zaditor™) was approved in the United States in 1999 for the temporary prevention of itching of the eye due to allergic conjunctivitis. Novartis Pharmaceuticals Corporation holds the NDA and markets the product in the United States and 60 countries worldwide.

In January 2006, the sponsor submitted a NDA with a new formulation of ketotifen fumarate, seeking FDA's approval on their product as an OTC drug. The new formulation and the marketed formulation are listed in the table below.

Component: standard quantity per ml (mg)	Standard quantity per ml (mg)	Marketed formulation	Function
Ketotifen fumarate	0.345 (equivalent to 0.25 mg ketotifen)	0.345	Active
Glycerin USP			
Benzalkonium chloride NF			
Sodium hydroxide, NF			
Hydrochloride acid, NF			
Water for injection, USP			

The sponsor indicated that since this is a 505(b)(2) application, they have not conducted nonclinical studies with the new formulation. Nonclinical studies performed by CIBA Vision (a predecessor company to Novartis) were referenced to support approval of this application.

A battery of toxicology studies, including one-year systemic toxicity studies in monkeys and dogs, 3-month systemic toxicity study in rats, and 6-month ocular toxicity study in rabbits, were conducted under NDA 21-066. No toxicologically significant findings were noted.

The new formulation contains Glycerin has been used in approved ophthalmic drugs with the concentrations of up to 3%. The sponsor has performed a clinical bioequivalence study demonstrating that the new formulation is "therapeutically equivalent to Zaditor™." Glycerin has been used in many drugs with different administration routes including oral, intravenous, topical ocular, or rectal route with the maximum daily dose of 120 g, much higher than the doses (up to 18 mg/day) proposed for this drug. It appears that systemic toxicity for glycerin should not be a concern. Since the drug with the new formulation was well-tolerated in the bioequivalence study, no nonclinical local tolerance studies are necessary.

Pregnancy Category C is listed in the current labeling for Zaditor™. The positive finding includes an increased incidence of retarded ossification of the sternebrae at 45 mg/kg/day of ketotifen.

This dose is 30,000 times of the maximum recommended human ocular dose. In addition, clinical studies showed that little systemic exposure to the drug is detected following ocular dosing. Considering the low dose (up to 75 µg/person/day), very low systemic exposure to the drug, and previous human experience, the pharmacology/toxicology reviewer considers that the drug exhibits no significant concerns regarding reproductive safety.

In conclusion, there are no outstanding pharmacology/toxicology issues for ketotifen fumarate. Approval is recommended for this NDA application from the pharmacology/toxicology viewpoint.

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/s/

Zhou Chen
5/17/2006 09:15:00 AM
PHARMACOLOGIST

Terry Peters
5/17/2006 11:10:18 AM
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