CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 21-066/S-001

Name: Zaditor (Ketotifen Fumarate Ophthalmic Solution) 0.025%

Sponsor: Ciba Vision

Approval Date: March 8, 2000

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-066/S-001

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-066/S-001

APPROVAL LETTER

NDA 21-066/S-001

Ciba Vision
Attention: Jeannie Skinner
Manager Regulatory Affairs
A Novartis Company
11460 Johns Creek Parkway
Duluth, GA 30097

MAR - 8 2000

Dear Ms. Skinner:

Please refer to your supplemental new drug application dated November 3, 1999, received November 5, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zaditor (ketotifen fumarate ophthalmic solution) 0.025%.

This supplemental new drug application provides for an additional paragraph in the Clinical Pharmacology section of the package insert.

We have completed the review of this supplemental application and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the labeling submitted November 3, 1999, with the revisions listed below. These revisions are terms of the NDA approval. Accordingly, the supplemental application is approved effective on the date of this letter.

As agreed in the telephone conversation on February 4, 2000, between you and Ms. Joanne Holmes of this Division, the following revisions will be made:

1. The established name will be revised to appear in lower case letters, as "ketotifen fumarate ophthalmic solution."

2. The second sentence of the second paragraph of the Clinical Pharmacology paragraph will begin "A study conducted with 15 healthy volunteers..."

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 21-066/S-001." Approval of this submission by FDA is not required before the labeling is used.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-40
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Joanne M. Holmes, M.B.A., Clinical Reviewer, at (301) 827-2090.

Sincerely,

WAC 3/8/00

Wiley A. Chambers, M.D.
Deputy Director
Division of Anti-Inflammatory, Analgesic and
Ophthalmic Drug Products, HFD-550
Office of Drug Evaluation V
Center for Drug Evaluation and Research

cc:
NDA 21-066 aw 2-7-00
HFD-550/Div. Files
HFD-550/Clin Rev/Holmes jh 2/7/00
HFD-550/Dep Dir/Chambers (with labeling) fNg 2/8/00
HFD-550/Proj Mgr/Rodriguez (with labeling) MR 2-7-00
HFD-880/Biopharm/Tandon (with labeling) for 2/7/00 VT 2/28/2000
HF-2/MedWatch (with labeling)
HFD-002/ORM (with labeling)
HFD-105/ADRA (with labeling)
HFD-104/Peds/V.Kao (with labeling)
HFD-40/DDMAC (with labeling)
HFI-20/Press Office (with labeling)
HFD-400/OPDRA (with labeling)
HFD-613/OGD (with labeling)
HFD-095/DDMS-IMT (with labeling)
DISTRICT OFFICE

Drafted by: jh/January 31, 2000
Initialed by:
final:
filename: 21066s1ap.doc

APPROVAL (AP)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-066/S-001

LABELING

APPROVED

MAR 8 2000

DRAFT PACKAGE INSERT TEXT ADDITION

Clinical Pharmacology

Ketotifen has been shown to have little systemic exposure following topical ocular administration. A study conducted with 15 volunteers dosed bilaterally with ketotifen fumarate ophthalmic solution twice daily for 14 days demonstrated plasma concentrations generally below the quantitation limit of assay (< 20 pg/mL).

CURENTLY APPROVED PACKAGE INSERT

APPROVED

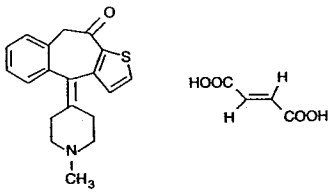
MAR 8 2000

ZADITOR™

Ketotifen Fumarate Ophthalmic Solution, 0.025%

0064

DESCRIPTION
ZADITOR™ is a sterile ophthalmic solution containing ketotifen for topical administration to the eyes. Ketotifen fumarate is a finely crystalline powder with an empirical formula of $C_{23}H_{23}NO_5S$ and a molecular weight of 425.50.



Established Name: Ketotifen Fumarate Ophthalmic Solution

CHEMICAL NAME
4-(1-Methyl-4-piperidylidene)-4*H*-benzo[4,5]cyclohepta[1,2-*b*] thiophen-10(9*H*)-one hydrogen fumarate

Each mL of ZADITOR™ contains: **Active:** 0.345 mg ketotifen fumarate equivalent to 0.25 mg ketotifen.
Inactives: glycerol, sodium hydroxide/hydrochloric acid (to adjust pH) and purified water.
Preservative: benzalkonium chloride 0.01%. It has a pH of 4.4 to 5.8 and an osmolality of 210-300 mOsm/kg.

CLINICAL PHARMACOLOGY
Ketotifen is a relatively selective, non-competitive histamine antagonist (H1-receptor) and mast cell stabilizer. Ketotifen inhibits the release of mediators from cells involved in hypersensitivity reactions. Decreased chemotaxis and activation of eosinophils has also been demonstrated.

In human conjunctival allergen challenge studies, ZADITOR™ was significantly more effective than placebo in preventing ocular itching associated with allergic conjunctivitis. The action of ketotifen occurs rapidly with an effect seen within minutes after administration.

INDICATIONS AND USAGE
ZADITOR™ (ketotifen fumarate ophthalmic solution) is indicated for the temporary prevention of itching of the eye due to allergic conjunctivitis.

CONTRAINDICTIONS
ZADITOR™ is contraindicated in persons with a known hypersensitivity to any component of this product.

WARNINGS
For topical ophthalmic use only. Not for injection or oral use.

PRECAUTIONS
Information for patients: To prevent contaminating the dropper tip and solution, care should be taken not to touch the eyelids or surrounding areas with the dropper tip of the bottle. Keep the bottle tightly closed when not in use. Patients should be advised not to wear a contact lens if their eye is red. ZADITOR™ should not be used to treat contact lens related irritation. The preservative in ZADITOR™, benzalkonium chloride, may be absorbed by soft contact lenses. Patients who wear soft contact lenses and whose eyes are not red, should be instructed to wait at least ten minutes after instilling ZADITOR™ before they insert their contact lenses.

Carcinogenesis, Mutagenesis, Impairment of Fertility:
Ketotifen fumarate was determined to be non-mutagenic in a battery of *in vitro* and *in vivo* mutagenicity assays including: Ames test, *in vitro* chromosomal aberration test with V79 Chinese hamster cells, *in vivo* micronucleus assay in mouse, and mouse dominant lethal test.

Treatment of male rats with oral doses of ketotifen ≥ 10 mg/kg/day orally [6,667 times the maximum recommended human ocular dose of 0.0015 mg/kg/day on a mg/kg basis (MRHOD)] for 70 days prior to mating resulted in mortality and a decrease in fertility. Treatment with ketotifen did not impair fertility in female rats receiving up to 50 mg/kg/day of ketotifen orally (33,333 times the MRHOD) for 15 days prior to mating.

Pregnancy: Pregnancy Category C
Oral treatment of pregnant rabbits during organogenesis with 45 mg/kg/day of ketotifen (30,000 times the MRHOD) resulted in an increased incidence of retarded ossification of the sternebrae. However, no effects were observed in rabbits treated with up to 15 mg/kg/day (10,000 times the MRHOD). Similar treatment of rats during organogenesis with 100 mg/kg/day of ketotifen (66,667 times the MRHOD) did not reveal any biologically relevant effects.

Oral treatment of pregnant rats (up to 100 mg/kg/day or 66,667 times the MRHOD) and rabbits (up to 45 mg/kg/day or 30,000 times the MRHOD) during organogenesis did not result in any biologically relevant embryofetal toxicity. In the offspring of the rats that received ketotifen orally from day 15 of pregnancy to day 21 post partum at 50 mg/kg/day (33,333 times the MRHOD), a maternally toxic treatment protocol, the incidence of postnatal mortality was slightly increased, and body weight gain during the first four days post partum was slightly decreased.

Nursing Mothers:
Ketotifen fumarate has been identified in breast milk in rats following oral administration. It is not known whether topical ocular administration could result in sufficient systemic absorption to produce detectable quantities in breast milk. Nevertheless, caution should be exercised when ketotifen fumarate is administered to a nursing mother.

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

ADVERSE REACTIONS
In controlled clinical studies, conjunctival injection, headaches, and rhinitis were reported at an incidence of 10 to 25%. The occurrence of these side effects was generally mild. Some of these events were similar to the underlying ocular disease being studied.

The following ocular and non-ocular adverse reactions were reported at an incidence of less than 5%:

Ocular: Allergic reactions, burning or stinging, conjunctivitis, discharge, dry eyes, eye pain, eyelid disorder, itching, keratitis, lacrimation disorder, mydriasis, photophobia, and rash.

Non-Ocular: Flu syndrome, pharyngitis.

OVERDOSAGE
Oral ingestion of the contents of a 5 mL bottle would be equivalent to 1.725 mg of ketotifen fumarate. Clinical results have shown no serious signs or symptoms after the ingestion of up to 20 mg of ketotifen fumarate.

DOSAGE AND ADMINISTRATION
The recommended dose is one drop in the affected eye(s) every 8 to 12 hours.

HOW SUPPLIED
ZADITOR™ is supplied as 5 mL solution in white 7.5 mL LDPE plastic bottles with controlled plastic dropper tips and white plastic caps.
NDC 58768-102-05

STORAGE
Store at 4°-25°C (39°-77°F)

℞ Only

Made in Canada by CIBA Vision Sterile Mfg. for
CIBA Vision®, A Novartis Company
Duluth, GA 30097

I6137-A J759F9

CIBA Vision.
A Novartis Company

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-066/S-001

MEDICAL REVIEW

FEB 4 2000

Clinical Review of NDA 21-066
Labeling Supplement

NDA 21-066/S-001

Submission Date:	11/3/99
Receipt Dates:	11/5/99
Review Date:	2/4/00

Applicant: Ciba Vision
A Novartis Company
11460 Johns Creek Parkway
Duluth, GA 30097

Applicant's Representative: Jeannie Skinner
Manager Regulatory Affairs
(678) 415-4343

Drug: Zaditor™ (ketotifen fumarate ophthalmic solution) 0.025%

Pharmacologic Class: Anti-histamine

Related Review: Clinical Pharmacology/Biopharmacology Review dated 1/6/00.

Submitted: Revised draft labeling to add a paragraph to the Clinical Pharmacology section. This paragraph reflects the results of the Phase 4 study to investigate the plasma levels of ketotifen fumarate after topical ophthalmic dosing of ketotifen fumarate ophthalmic solution 0.025%. Ciba submitted a copy of the currently approved insert and a page with the proposed additional paragraph.

Following is the proposed paragraph submitted by the company. Reviewer recommended deletions are noted by ~~strikeout~~ and additions by double underline within the review.

Ketotifen has been shown to have little systemic exposure following topical ocular administration. A study conducted with 15 healthy volunteers dosed bilaterally with ketotifen fumarate ophthalmic solution twice daily for 14 days demonstrated plasma concentrations generally below the quantitation limit of assay (<20 pg/mL).

Reviewer's comments: *Ciba proposes to insert the paragraph above based on the results of a clinical PK study. Per the biopharmacology review dated 1/6/00, this is acceptable with the insertion noted. This will be the second paragraph in the Clinical Pharmacology section.*

Recommendation: An approval letter, requesting final printed labeling of the package insert, is recommended, with the following 2 revisions:

1. The established name should be revised to appear in lower case letters, as "ketotifen fumarate ophthalmic solution."
2. The second sentence of the second paragraph of the Clinical Pharmacology paragraph should begin "A study conducted with 15 healthy volunteers..."

These revisions were agreed to in a telephone conversation with Ms. Skinner on 2/4/00.

Joanne M. Holmes

Wiley A. Chambers, M.D.

cc:
NDA 21-066
HFD-550 Div Files
HFD-550/Dep Dir/Chambers
HFD-550/Proj Mgr/Rodriguez
HFD-550/Clin Rev/Holmes

21066s1rev.doc

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-066/S-001

CLINICAL PHARMACOLOGY / BIOPHARMACEUTICS REVIEW

18.1

Clinical Pharmacology/Biopharmaceutics Review

JAN 6 2000

NDA: 21-066 (~~SLR002~~ SLR-001) SUBMISSION DATE: 11/5/99

PRODUCT: ZADITOR™
Ketotifen fumarate
Ophthalmic solution (0.025%)

SPONSOR: Ciba Vision
GA 30097

REVIEWER: Veneeta Tandon, Ph.D.

Phase IV Commitment

Background

ZADITOR™, ketotifen fumarate ophthalmic solution (0.025%) has recently been approved for the prevention of ocular symptoms associated with seasonal allergic conjunctivitis. Ciba Vision has conducted a clinical study to determine the systemic absorption of ketotifen in accordance to their phase IV commitment made with this NDA.

Compared to systemic use, topical administration of 1 drop (~30μL) of 0.025% ketotifen fumarate ophthalmic solution twice daily in each eye corresponds to 1.5% of a recommended oral daily dose.

The study conducted is:

Protocol No. C-08-99-005: "*A study of the pharmacokinetics of ketotifen fumarate 0.025% ophthalmic solution following topical ocular administration over a 14-day period in healthy adults*".

Clinical Site	Dr. Irving E. Weston MDS Harris, Phoenix Arizona
Study Design:	Single Center, open label study
Dose:	BID application of 0.025% ketotifen fumarate ophthalmic solution to each eye for 14 days (lot no. 80749).
Population:	18 healthy subjects (9F & 9M, 16 were Caucasian and 2 Hispanic). The mean age of subjects was 48 years (range 22-76), mean weight was 77.4 kg (range 56.8-119.9). 15 subjects completed the study.

Out of the other 3, one discontinued due to personal reasons and 2 had protocol violations. The demographic information is attached on page 5.

Blood sampling: On Day 1 after single dose and on Day 14 after multiple-doses at the following time points; 10 minutes predose and at 15, 30, 45 minutes postdose and 1, 2, 3, 4, 6, and 8 hours postdose. A total of 300 plasma samples were collected from 15 subjects.

Analytical Validation: *Methodology*: LC/MS/MS, internal standard was (b) (4)
Limit of quantification: 20 pg/mL (range 20-250 pg/mL)
Inter-assay accuracy: within –6.39 to 7.10% of the nominal value
Inter-assay precision: % CV 1.8-3.1%
Intra-assay precision: %CV between 1-8%.
Recovery: 67.5 ± 15.3%
Stability: plasma samples for 2 hours at room temperature and extracted samples for 12 hours in autosampler

Pharmacokinetic Results: Only 2 out of 300 plasma samples had detectable levels of ketotifen fumarate. The two quantifiable levels were 25 and 79 pg/mL. The values 79 pg/mL occurred at predose and could not be explained. 25 pg/mL was detected at 3 hours after a single ocular dosing on Day 1.
Another subjects had levels of 20 and 24 pg/mL at 313 and 314 hours after dosing. However, QC20's of that day had failed and the LOQ was set to 60 pg/mL for that day.
The plasma concentration data for each subject is attached on pages 6-7.

Conclusions: The systemic absorption of ketotifen was very minimal following single ocular administration and even after multiple dosing for 14 Days.

Recommendation: The sponsors proposed addition to the clinical pharmacology section of the label is acceptable, with the addition of the word "healthy" after 15 on line second, to read as "15 healthy volunteers". A copy of the text addition is attached on page 8.

Veneeta Tandon 12/23/99
Veneeta Tandon, Ph.D.
Pharmacokineticist
Division of Pharmaceutical Evaluation III

Team Leader: E. Dennis Bashaw, Pharm. D. EB 1/6/00

CC: NDA 21-066
HFD-550/Div File
HFD-550/CSO/Rodriguez
HFD-880(Bashaw/Tandon)
HFD-880(Lazor)
HFD-344(Viswanathan)
CDR ATTN: B.Murphy

APPENDIX
N 21-066

Table 14.1.2. Demographic Information for All Subjects

Subject Number	Initials	Randomized Treatment	Treatment Received	Gender	Age (Years)	Height (cm)	Weight (kg)	Frame	Smoking Habits	Race	Completed Study According to Protocol?	Included in Safety Analysis ?	Included in PK Analysis ?
1	(b)	A	A	FEMALE	64	170	64.9	Medium	NONSMOKER-QUIT 1980.	HISPANIC	YES	YES	YES
2	(6)	A	A	FEMALE	22	168	88.5	Medium	NONSMOKER	CAUCASIAN	YES	YES	YES
3		A	A	FEMALE	50	173	60.4	Medium	NONSMOKER-QUIT 06/98.	CAUCASIAN	YES	YES	YES
4		A	A	MALE	31	191	106.7	Large	NONSMOKER	CAUCASIAN	YES	YES	YES
5		A	A	MALE	52	180	94.4	Large	NONSMOKER	CAUCASIAN	YES	YES	NO
6		A	A	FEMALE	71	157	66.7	Large	NONSMOKER-QUIT 1959.	CAUCASIAN	YES	YES	YES
7		A	A	FEMALE	65	168	60.8	Small	NONSMOKER	CAUCASIAN	YES	YES	YES
8		A	A	MALE	28	183	64	Medium	NONSMOKER	CAUCASIAN	YES	YES	YES
9		A	A	MALE	35	185	119.9	Large	NONSMOKER	CAUCASIAN	NO	YES	NO
10		A	A	MALE	46	188	94.4	Large	NONSMOKER	CAUCASIAN	YES	YES	YES
11		A	A	FEMALE	37	168	66.3	Small	NONSMOKER	CAUCASIAN	YES	YES	YES
12		A	A	FEMALE	61	152	57.2	Large	NONSMOKER	CAUCASIAN	YES	YES	YES
13		A	A	FEMALE	54	160	56.8	Medium	NONSMOKER	CAUCASIAN	YES	YES	YES
14		A	A	MALE	37	188	63.1	Large	NONSMOKER-QUIT 01/83.	CAUCASIAN	YES	YES	YES
15		A	A	MALE	23	185	69.5	Small	NONSMOKER.	HISPANIC	YES	YES	YES
16		A	A	FEMALE	44	170	82.6	Medium	NONSMOKER-QUIT 02/89.	CAUCASIAN	YES	YES	YES
17		A	A	MALE	76	180	89.9	Large	NONSMOKER	CAUCASIAN	YES	YES	YES
18		A	A	MALE	59	183	87.2	Medium	NONSMOKER	CAUCASIAN	YES	YES	NO

Treatment A = 0.025% Ketotifen Fumarate Ophthalmic Solution

14.2 Pharmacokinetic/Efficacy Data

Table 14.2.1. Plasma Ketotifen Concentrations (pg/mL) Following Single Dose of One Drop of Ketotifen Fumarate 0.025% Ophthalmic Solution Into Each Eye

Subject Number	Treatment Sequence	Study Period	Sample Times (hr) 0	0.25	0.5	0.75	1	2	3	4	6	8
1	A	1	0	0	0	0	0	0	0	0	0	0
2	A	1	0	0	0	0	0	0	25	0	0	0
3	A	1	0	0	0	0	0	0	0	0	0	0
4	A	1	0	0	0	0	0	0	0	0	0	0
6	A	1	0	0	0	0	0	0	0	0	0	0
7	A	1	0	0	0	0	0	0	0	0	0	0
8	A	1	79	0	0	0	0	0	0	0	0	0
10	A	1	0	0	0	0	0	0	0	0	0	0
11	A	1	0	0	0	0	0	0	0	0	0	0
12	A	1	0	0	0	0	0	0	0	0	0	0
13	A	1	0	0	0	0	0	0	0	0	0	0
14	A	1	0	0	0	0	0	0	0	0	0	0
15	A	1	0	0	0	0	0	0	0	0	0	0
16	A	1	0	0	0	0	0	0	0	0	0	0
17	A	1	0	0	0	0	0	0	0	0	0	0
Mean			5	0	0	0	0	0	2	0	0	0
S.D.			20	0	0	0	0	0	7	0	0	0
C.V.(%)			387	.	.	.	.	.	387	.	.	.
S.E.M.			5	0	0	0	0	0	2	0	0	0
N			15	15	15	15	15	15	15	15	15	15
Minimum			0	0	0	0	0	0	0	0	0	0
Maximum			79	0	0	0	0	0	25	0	0	0

Samples below the quantifiable limit of 20 are reported as 0

Table 14.2.2. Plasma Ketotifen Concentrations (pg/mL) Following Multiple Dose of One Drop of Ketotifen Fumarate 0.025% Ophthalmic Solution Into Each Eye

Subject Number	Treatment Sequence	Study Period	Sample Times (hr) 311.83	312.25	312.5	312.75	313	314	315	316	318	320
1	A	1	0	0	0	0	0	0	0	0	0	0
2	A	1	0	0	0	0	0	0	0	0	0	0
3	A	1	0	0	0	0	0	0	0	0	0	0
4	A	1	0	0	0	0	0	0	0	0	0	0
6	A	1	0	0	0	0	0	0	0	0	0	0
7	A	1	0	0	0	0	0	0	0	0	0	0
8	A	1	0	0	0	0	0	0	0	0	0	0
10	A	1	0	0	0	0	0	0	0	0	0	0
11	A	1	0	0	0	0	0	0	0	0	0	0
12	A	1	0	0	0	0	0	0	0	0	0	0
13	A	1	0	0	0	0	0	0	0	0	0	0
14	A	1	0	0	0	0	0	0	0	0	0	0
15	A	1	0	0	0	0	0	0	0	0	0	0
16	A	1	0	0	0	0	0	0	0	0	0	0
17	A	1	0	0	0	0	0	0	0	0	0	0
Mean			0	0	0	0	0	0	0	0	0	0
S.D.			0	0	0	0	0	0	0	0	0	0
C.V.(%)			.	.	.	.	.	.	.	.	.	.
S.E.M.			0	0	0	0	0	0	0	0	0	0
N			15	15	15	15	15	15	15	15	15	15
Minimum			0	0	0	0	0	0	0	0	0	0
Maximum			0	0	0	0	0	0	0	0	0	0

Samples below the quantifiable limit of 20 are reported as 0.

DRAFT PACKAGE INSERT TEXT ADDITION

Clinical Pharmacology

Ketotifen has been shown to have little systemic exposure following topical ocular administration. A study conducted with 15 volunteers dosed bilaterally with ketotifen fumarate ophthalmic solution twice daily for 14 days demonstrated plasma concentrations generally below the quantitation limit of assay (< 20 pg/mL).

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-066/S-001

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

NDA NO. 21-066 REF NO. 001
NDA SUPPL FOR SLR

SUPPL NC & SLR 001 (NC)

ORIGINAL

CIBA Vision®
A Novartis Company

November 3, 1999

CIBA Vision Corporation
U.S. Ophthalmics
11460 Johns Creek Parkway
Duluth, Georgia 30097-1556

Wiley Chambers, M.D., Deputy Director
Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products, HFD-550
Office of Drug Evaluation 5, CDER
Food and Drug Administration
9201 Corporate Boulevard - Building 2 - Floor 2N
Gaithersburg, MD 20850-3202

RE: NDA 21-066: Zaditor™
(Ketotifen Fumarate 0.025% Ophthalmic Solution)
Prior Approval Supplement
Phase IV Commitments, Draft Labeling

Dear Dr. Chambers:

Please find the attached submission which contains 2 volumes. The first volume contains a clinical pharmacokinetics study report for ketotifen fumarate ophthalmic solution and the second a draft package insert for approval. The clinical report fulfills CIBA Vision's commitment as stated in the June 21, 1999 amendment, Issue 1. The commitment stated that CIBA Vision would conduct a clinical study to determine the absorption of ketotifen after dosing with ketotifen fumarate ophthalmic solution.

The enclosed report "A Study of the Pharmacokinetics of Ketotifen Fumarate 0.025% Ophthalmic Solution Following Topical Ocular Administration Over a Fourteen Day Period in Healthy Adults" indicates that ketotifen concentrations in the majority of the plasma samples analyzed were below the limit of quantitation of the LC/MS/MS bioanalytical assay. There was little evidence of systemic absorption of ketotifen following ocular instillation after repeated dosing for 14 days. Ocular administration of ketotifen fumarate ophthalmic solution was safe and well tolerated by the study population. There were 28 adverse events experienced by 8 of the 18 subjects dosed with the study drug. The majority of the adverse events were considered mild in severity and there were no serious adverse events.

The draft package insert text includes a summary of the above study in the Clinical Pharmacology section that will be inserted as paragraph 2. No other changes to the insert have been made. For your ease in review a copy of the currently approved package insert has been included. The additional text is as follows:

> Ketotifen has been shown to have little systemic exposure following topical ocular administration. A study conducted with 15 volunteers dosed bilaterally with ketotifen fumarate ophthalmic solution twice daily for 14 days demonstrated plasma concentrations generally below the quantitation limit of assay (< 20 pg/mL).

CIBA Vision®
A Novartis Company

CIBA Vision Corporation
U.S. Ophthalmics
11460 Johns Creek Parkway
Duluth, Georgia 30097-1556

If there are any questions or if additional information is required regarding this report, please contact the undersigned at the above address or by telephone at (678) 415-4343.

Sincerely,

David M. Dobrowski
Sr. Regulatory Affairs Associate

Food and Drug Administration
Rockville MD 20857

NDA 21-066/S-001

Ciba Vision
11460 Johns Creek Parkway
Duluth, GA 30097

FEB 10 2000

Attention: Ms. Jeannie Skinner, Manager Regulatory Affairs

Dear Ms. Skinner:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: Zaditor™ (ketotifen fumarate) 0.025% Ophthalmic Solution

NDA Number: 21-066

Supplement Number: S-001

Date of Supplement: November 3, 1999

Date of Receipt: November 5, 1999

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on January 4, 2000, in accordance with 21 CFR 314.101(a).

All communications concerning this NDA should be addressed as follows:

Food and Drug Administration
Division of Anti-Inflammatory, Analgesic and
Ophthalmic Drug Products, HFD-550
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Attention: Document Control Room
5600 Fishers Lane
Rockville, MD 20857

Sincerely,

2/7/2000

For Leslie Vaccari
Acting Chief, Project Management Staff
Division of Anti-Inflammatory, Analgesic and
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Office of Drug Evaluation V
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cc:
Original NDA 21-066/S-001
HFD-550/Div. Files
HFD-550/CSO/R. Rodriguez

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