CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: **21-066**

CORRESPONDENCE

VIA AIRBORNE EXPRESS

CIBA Vision
A Novartis Company

December 31, 1998

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

Central Document Room
Center for Drug Evaluation and Research
Food and Drug Administration
12229 Wilkins Avenue
Rockville, Maryland 20852

Attention: Wiley Chambers, M.D., Deputy Director
Division of Anti-Inflammatory, Analgesic and Ophthamic Drug Products,
HFD-550

RE: NDA 21-066
Ketotifen fumarate ophthalmic solution

Dear Dr. Chambers:

CIBA Vision is pleased to submit a New Drug Application for ketotifen fumarate ophthalmic solution (0.025% ketotifen base) under the provisions of 21 CFR 314.50 and Section 505 (b)(1) of the Federal Food, Drug and Cosmetic Act.

Included in this submission is one complete archival copy (Volumes 1 through 49) and review copies for each section as required in colored jackets. Also included are six copies of the Summary Volume for each of the six technical reviewers.

Per the request of the Division, eighteen desk copies of the Summary Volume are being forwarded under separate cover to Raphael Rodriguez, Project Manager. As committed to the Division, electronic copies of available files will also be provided. The electronic versions will be identical to the paper copy provided in this submission.

CIBA Vision certifies that a true copy of the Chemistry, Manufacturing and Controls, Microbiology and Samples, Methods Validation and Labeling sections of this NDA are being provided to the Atlanta District of the Food and Drug Administration to the attention of Ballard Graham.

If there are any questions regarding this submission, please contact the undersigned at (770) 418-4343.

Sincerely,

Stacey E Huntsinger

Stacey Huntsinger RAC
Sr. International Regulatory Associate

HFO-550 Rodriguez

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-066

JAN 14 1999

Ciba Vision - A Novartis Company
Attention: Lawrence D. Mandt
Director, US Regulatory & Medical Affairs
11460 Johns Creek Parkway
Duluth, GA 30097

Dear Mr. Mandt:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Ketotifen Fumarate (fumarate ophthalmic solution) Ophthalmic Solution 0.025%

Therapeutic Classification: Priority (P)

Date of Application: December 31, 1998

Date of Receipt: January 4, 1999

Our Reference Number: NDA 21-066

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on March 5, 1999, in accordance with 21 CFR 314.101(a).

Under 21 CFR 314.102(c) of the new drug regulations, you may request an informal conference with this Division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the application's ultimate approvability. Alternatively, you may choose to receive such a report by telephone.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed as follows:

U.S. Postal Service:

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

Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-Inflammatory, Analgesic and Ophthalmic Drug Products, HFD-550
Attention: Division Document Room
9201 Corporate Blvd.
Rockville, Maryland 20850-3202

If you have any questions, contact Raphael R. Rodriguez, Project Manager, at (301) 827-2090.

Sincerely,

/S/

Anthony M. Zeccola
Chief, Project Management Staff
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
HFD-550/Div. Files
HFD-550/R. Rodriguez 1/8/99
HFD-550/DepDir/Chambers
DISTRICT OFFICE

Drafted by: rrr/January 8, 1999

ACKNOWLEDGEMENT (AC)

CIBA Vision.
A Novartis Company

VIA FEDERAL EXPRESS
NDA 21-066

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

February 1, 1999

Wiley Chambers, M.D., Deputy Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-Inflammatory, Analgesic, and
Ophthalmic Drug Products, HFD-550
Attention: Division Document Room
9201 Corporate Boulevard
Rockville, MD 20850-3202

RE: NDA 21-066 - Ketotifen Fumarate Ophthalmic Solution
General Correspondence - Request for Trade Name Review

Dear Dr. Chambers:

CIBA Vision hereby requests review and comment by the CDER Labeling and Nomenclature Committee on the trade name [redacted] for the drug, ketotifen fumarate ophthalmic solution, that is proposed for use in allergic conjunctivitis. This drug was the subject of NDA 21-066 submitted to FDA on December 31, 1998.

Appropriate legal clearance screening searches were performed to ensure that no marks or producer names in the US could be confused with the trade name [redacted] No opposing name was identified in the search and no opposition was filed.

Proposed trade name:	[redacted]
Established name (USAN):	ketotifen fumarate
Dosage form:	ophthalmic solution
Common name:	ketotifen

If there are questions or comments regarding this submission, please contact the undersigned at (770) 418-4343.

Sincerely,

Stacey Huntsinger, RAC
Sr. International Regulatory Associate

Desk copy: Raphael Rodriguez, Project Manager (via fax)

VIA FEDERAL EXPRESS
NDA 21-066

ORIGINAL

CIBA Vision
A Novartis Company

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

February 3, 1999

NDA ORIG AMENDMENT
BL

Wiley Chambers, M.D., Deputy Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-Inflammatory, Analgesic, and
Ophthalmic Drug Products, HFD-550
Attention: Division Document Room
9201 Corporate Boulevard
Gaithersburg, MD 20850-3202

Noted
2/17/99
ID 10748

RE: NDA 21-066 - Ketotifen Fumarate Ophthalmic Solution
NDA Amendment – Response to Preclinical Issues

Dear Dr. Chambers:

In response to a 01-26-99 facsimile from the Division regarding NDA 21-066 for ketotifen fumarate ophthalmic solution, please find attached an amendment to the NDA that addresses the preclinical issues raised. The original NDA for ketotifen fumarate ophthalmic solution was filed on December 31, 1998.

If there are questions or comments regarding this submission, please contact the undersigned at (770) 418- 4343.

Sincerely,

Stacey E Huntsinger

Stacey Huntsinger, RAC
Sr. International Regulatory Associate

Desk copy: R. Rodriguez, Project Manager (via fax)

VIA FEDERAL EXPRESS
NDA 21-066

ORIGINAL

CIBA Vision.
A Novartis Company

February 3, 1999

NDA ORIG AMENDMENT

BC

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

Wiley Chambers, M.D., Deputy Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-Inflammatory, Analgesic, and
Ophthalmic Drug Products, HFD-550
Attention: Division Document Room
9201 Corporate Boulevard
Gaithersburg, MD 20850-3202

RE: NDA 21-066 - Ketotifen Fumarate Ophthalmic Solution
NDA Amendment – Response to CMC issues

Dear Dr. Chambers:

In response to a 01-22-99 facsimile from the Division regarding NDA 21-066 for ketotifen fumarate ophthalmic solution, please find attached an amendment to the NDA that addresses the technical issues raised. The original NDA for ketotifen fumarate ophthalmic solution was filed on December 31, 1998.

If there are questions or comments regarding this submission, please contact the undersigned at (770) 418- 4343.

Sincerely,

Stacey Huntsinger

Stacey Huntsinger, RAC
Sr. International Regulatory Associate

Desk copy: R. Rodriguez, Project Manager (via fax)

VIA FEDERAL EXPRESS
NDA 21-066

CIBA Vision.
A Novartis Company

February 5, 1999

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

Wiley Chambers, M.D., Deputy Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-Inflammatory, Analgesic, and
Ophthalmic Drug Products, HFD-550
Attention: Division Document Room
9201 Corporate Boulevard
Rockville, MD 20850-3202

RE: NDA 21-066 - Ketotifen Fumarate Ophthalmic Solution
NDA Amendment – Response to Statistical Issues

Dear Dr. Chambers:

In response to a 01-27-99 facsimile from the Division regarding NDA 21-066 for ketotifen fumarate ophthalmic solution, please find attached an amendment to the NDA that addresses the statistical issues raised. The original NDA for ketotifen fumarate ophthalmic solution was filed on December 31, 1998.

If there are questions or comments regarding this submission, please contact the undersigned at (770) 418- 4343.

Sincerely,

Stacey Huntsinger

Stacey Huntsinger, RAC
Sr. International Regulatory Associate

Desk copy: R. Rodriguez, Project Manager

VIA FEDERAL EXPRESS
NDA 21-066

CIBA Vision.
A Novartis Company

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

February 9, 1999

Wiley Chambers, M.D., Deputy Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-Inflammatory, Analgesic, and
Ophthalmic Drug Products, HFD-550
Attention: Division Document Room
9201 Corporate Boulevard
Rockville, MD 20850-3202

RE: NDA 21-066 - Ketotifen Fumarate Ophthalmic Solution
NDA Amendment – 2nd Response to Statistical Issues

Dear Dr. Chambers:

In response to a 01-27-99 facsimile from the Division regarding NDA 21-066 for ketotifen fumarate ophthalmic solution, an amendment was filed to NDA 21-066 on 02-05-99. Please find attached a second amendment to the NDA that addresses the remaining statistical issues raised in the 01-27-99 facsimile. The original NDA for ketotifen fumarate ophthalmic solution was filed on December 31, 1998.

If there are questions or comments regarding this submission, please contact the undersigned at (770) 418- 4343.

Sincerely,

Stacey Huntsinger

Stacey Huntsinger, RAC
Sr. International Regulatory Associate

Desk copy: R. Rodriguez, Project Manager

CIBA Vision.
A Novartis Company

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

VIA FEDERAL EXPRESS
NDA 21-066

February 10, 1999

Wiley Chambers, M.D., Deputy Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-Inflammatory, Analgesic, and
Ophthalmic Drug Products, HFD-550
Attention: Division Document Room
9201 Corporate Boulevard
Gaithersburg, MD 20850-3202

RE: NDA 21-066 - Ketotifen Fumarate Ophthalmic Solution
General Correspondence

Dear Dr. Chambers:

In response to a 02-03-99 request from the Division, please find attached a table that states the readiness of CIBA Vision and Novartis facilities involved in the manufacture and/or testing of ketotifen fumarate ophthalmic solution with their respective CFN numbers. The statement that CIBA Vision Sterile Manufacturing would prefer inspection after March 1, 1999 has been removed.

If there are questions or comments regarding this submission, please contact the undersigned at (770) 418- 4343.

Sincerely,

Stacey Huntsinger

Stacey Huntsinger, RAC
Sr. International Regulatory Associate

Desk copy: R. Rodriguez, Project Manager (via fax)

VIA FEDERAL EXPRESS
NDA 21-066

CIBA Vision.
A Novartis Company

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

February 15, 1999

Wiley Chambers, M.D., Deputy Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-Inflammatory, Analgesic, and
Ophthalmic Drug Products, HFD-550
Attention: Division Document Room
9201 Corporate Boulevard
Rockville, MD 20850-3202

RE: NDA 21-066 - Ketotifen Fumarate Ophthalmic Solution
NDA Amendment – Electronic copies of clinical information

Dear Dr. Chambers:

In response to 02-12-99 request from the Division regarding NDA 21-066 for ketotifen fumarate ophthalmic solution, please find enclosed disk copies of the following clinical information:

Disk 1
Clinical Trial Report C-08-97-001: A Dose-Response Evaluation of Ketotifen Fumarate Ophthalmic Solution in Varying Concentrations Against Placebo Control in the Allergen Challenge Model

Disk 2
Clinical Trial Report C-08-97-002: Safety and Efficacy of Ketotifen Fumarate 0.025% Ophthalmic Solution Compared with Vehicle Placebo Control in the Allergen Challenge Model of Allergic Conjunctivitis

Disk 3
Clinical Trial Report C-08-97-003: Six-Week Safety Trial of Ketotifen Fumarate 0.025% Ophthalmic Solution in Volunteers with Normal Ocular Health

Disk 4
Clinical Trial Report C-08-97-004: Safety and Efficacy of Ketotifen Fumarate 0.025% Ophthalmic Solution Compared with Vehicle Placebo Control in the Allergen Challenge Model of Allergic Conjunctivitis

Disk 5
Integrated Summary of Efficacy
Integrated Summary of Safety
Draft Package Insert

The information provided on these disks is in Word 7.0 format. The files are not compressed. The files contain only the text portions of each document and are identical to the paper copies of the text provided in the original NDA submission of 12-31-98.

If there are questions or comments regarding this submission, please contact the undersigned at (770) 418- 4343.

Sincerely,

Stacey E Huntsinger

Stacey Huntsinger, RAC
Sr. International Regulatory Associate

Desk copy: R. Rodriguez, Project Manager

APPEARS THIS WAY
ON ORIGINAL

CIBA Vision.
A Novartis Company

VIA FEDERAL EXPRESS
NDA 21-066

February 18, 1999

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

Wiley Chambers, M.D., Deputy Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-Inflammatory, Analgesic, and
Ophthalmic Drug Products, HFD-550
Attention: Division Document Room
9201 Corporate Boulevard
Rockville, MD 20850-3202

RE: NDA 21-066 - Ketotifen Fumarate Ophthalmic Solution
NDA Amendment – Response to Preclinical Question

Dear Dr. Chambers:

In response to a 02-18-99 telephone request from the Division regarding NDA 21-066 for ketotifen fumarate ophthalmic solution, this amendment clarifies the use of DR numbers for formulations used in research and development. This information should be forwarded to Dr. Chen.

If there are questions or comments regarding this submission, please contact the undersigned at (770) 418- 4343.

Sincerely,

Stacey E Huntsinger

Stacey Huntsinger, RAC
Sr. International Regulatory Associate

Desk copy: R. Rodriguez, Project Manager (via fax)

CIBA Vision.
A Novartis Company

VIA FEDERAL EXPRESS
NDA 21-066

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

February 22, 1999

Wiley Chambers, M.D., Deputy Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-Inflammatory, Analgesic, and
Ophthalmic Drug Products, HFD-550
Attention: Division Document Room
9201 Corporate Boulevard
Rockville, MD 20850-3202

RE: NDA 21-066 - Ketotifen Fumarate Ophthalmic Solution
NDA Amendment – Response to Preclinical Question

Dear Dr. Chambers:

In response to a 02-22-99 telephone request from the Division regarding NDA 21-066 for ketotifen fumarate ophthalmic solution, this amendment clarifies the use of degraded ketotifen fumarate ophthalmic solution in the following preclinical study:

Leuschner, J. 13-week ocular tolerance and subchronic toxicity study of heat-degraded DR42013 by instillation into the conjunctival sac of albino rabbits. LPT [redacted] Report 10866/1/97, 12-Oct-98.

Additionally, this amendment includes copies of preclinical information requested by the Division in a facsimile dated 01-26-99. An electronic copy of the text portion of section 5 of the NDA has been attached for the reviewer's convenience. This electronic copy does not include any attachments (i.e. study reports). However, it is an identical copy of the text portion of section 5 of NDA 21-066 for ketotifen fumarate ophthalmic solution. The original NDA was filed on December 31, 1998.

The information included in this amendment should be forwarded to Dr. Chen. If there are questions or comments regarding this submission, please contact the undersigned at (770) 418- 4343.

Sincerely,

Stacey Huntsinger, RAC
Sr. International Regulatory Associate

Desk copy: R. Rodriguez, Project Manager (via fax)

APPEARS THIS WAY
ON ORIGINAL

ORIGINAL

CIBA Vision.
A Novartis Company

VIA FEDERAL EXPRESS
NDA 21-066

NEW CORRESP
NC

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

February 24, 1999

Noted 3/8/99
ID 10804

Wiley Chambers, M.D., Deputy Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-Inflammatory, Analgesic, and
Ophthalmic Drug Products, HFD-550
Attention: Division Document Room
9201 Corporate Boulevard
Rockville, MD 20850-3202

RE: NDA 21-066 - Ketotifen Fumarate Ophthalmic Solution
General Correspondence

Dear Dr. Chambers:

CIBA Vision commits to providing the additional information requested for the carcinogenicity studies (i.e. reformatted data) submitted in NDA 21-066 for ketotifen fumarate ophthalmic solution by the end of March 1999. It is acknowledged that this request for additional information was made both at the pre-NDA meeting in September 1998 and in a facsimile dated 01-26-99.

If there are questions or comments regarding this submission, please contact the undersigned at (770) 418- 4343.

Sincerely,

Stacey Huntsinger

Stacey Huntsinger, RAC
Sr. International Regulatory Associate

Desk copy: R. Rodriguez, Project Manager

CIBA Vision.
A Novartis Company

VIA FEDERAL EXPRESS
NDA 21-066

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

February 26, 1999

Wiley Chambers, M.D., Deputy Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-Inflammatory, Analgesic, and
Ophthalmic Drug Products, HFD-550
Attention: Division Document Room
9201 Corporate Boulevard
Rockville, MD 20850-3202

RE: NDA 21-066 - Ketotifen Fumarate Ophthalmic Solution
Amendment – Environmental Assessment

Dear Dr. Chambers:

In response to a request from the Division regarding NDA 21-066, this amendment clarifies how the disposal of manufacturing and laboratory waste for ketotifen fumarate ophthalmic solution is handled. This information is presented as an amendment to the Environmental Assessment submitted in the original NDA dated December 31, 1998. A copy of the Environmental Assessment is attached for the reviewer's reference.

If there are questions or comments regarding this submission, please contact the undersigned at (770) 418- 4343.

Sincerely,

Stacey E Huntsinger

Stacey Huntsinger, RAC
Sr. International Regulatory Associate

Desk copy: R. Rodriguez, Project Manager (via fax)

CIBA Vision.
A Novartis Company

VIA FEDERAL EXPRESS
NDA 21-066

CIBA Vision Corporation
U.S. Ophthalmics
11460 Johns Creek Parkway
Duluth, Georgia 30097-1536

March 4, 1999

Wiley Chambers, M.D., Deputy Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-Inflammatory, Analgesic, and
Ophthalmic Drug Products, HFD-550
Attention: Division Document Room
9201 Corporate Boulevard
Rockville, MD 20850-3202

RE: NDA 21-066 - Ketotifen Fumarate Ophthalmic Solution
NDA Amendment – Preclinical Information

Dear Dr. Chambers:

In response to a request from the Division made during the pre-NDA meeting for ketotifen fumarate ophthalmic solution, this amendment provides the report for the following study:

Micronucleus Test of Ketotifen Fumarate in Bone Marrow Cells of the NMRI Mouse by Intravenous Administration

Based upon the findings of this recently conducted study, ketotifen fumarate showed no mutagenic properties at the two tested sampling points, tested up to the maximum tolerated dose level of 12 mg/kg b.w. i.v. In the same system, cyclophosphamide induced significant damage.

Also included in this amendment is a full copy of an additional study report:

Acute Oral Toxicity Studies of [redacted] Syrup in Rats (01-25-80)

This report is being provided as the copy originally submitted in [redacted] was of poor quality. The best copy available is being provided with this submission.

The information included in this amendment should be forwarded to Dr. Chen. If there are questions or comments regarding this submission, please contact the undersigned at (770) 418- 4343.

Sincerely,

Stacey Huntsinger

Stacey Huntsinger, RAC
Sr. International Regulatory Associate

Desk copy: R. Rodriguez, Project Manager

APPEARS THIS WAY
ON ORIGINAL

DUPLICATE

CIBA Vision.
A Novartis Company

VIA FEDERAL EXPRESS
NDA 21-066

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

NDA ORIG AMENDMENT

March 5, 1999

Wiley Chambers, M.D., Deputy Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-Inflammatory, Analgesic, and
Ophthalmic Drug Products, HFD-550
Attention: Division Document Room
9201 Corporate Boulevard
Rockville, MD 20850-3202

RE: NDA 21-066 - Ketotifen Fumarate Ophthalmic Solution
NDA Amendment – Response to Microbiology Questions

Dear Dr. Chambers:

In response to a 02-22-99 facsimile from the Division regarding NDA 21-066 for ketotifen fumarate ophthalmic solution, please find attached an amendment to the NDA that addresses the microbiological issues raised. The original NDA for ketotifen fumarate ophthalmic solution was filed on December 31, 1998.

If there are questions or comments regarding this submission, please contact the undersigned at (770) 418- 4343.

Sincerely,

Stacey Huntsinger

Stacey Huntsinger, RAC
Sr. International Regulatory Associate

Desk copy: R. Rodriguez, Project Manager

DUPLICATE

VIA FEDERAL EXPRESS
NDA 21-066

NDA ORIG AMENDMENT
BM

March 10, 1999

CIBA Vision.
A Novartis Company

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

Wiley Chambers, M.D., Deputy Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-Inflammatory, Analgesic, and
Ophthalmic Drug Products, HFD-550
Attention: Division Document Room
9201 Corporate Boulevard
Gaithersburg, MD 20850-3202

RE: NDA 21-066 - Ketotifen Fumarate Ophthalmic Solution
NDA Amendment – Response to Preclinical Issue

Dear Dr. Chambers:

In response to a 01-26-99 facsimile from the Division regarding NDA 21-066 for ketotifen fumarate ophthalmic solution, please find attached an amendment to the NDA that provides a legible copy of the following requested information:

Griffith, RW and Hodel, C: One Year Oral Toxicity Study in Beagle Dogs, February 27, 1976. ***(Tables 5, 20 and 37)***

If there are questions or comments regarding this submission, please contact the undersigned at (770) 418- 4343.

Sincerely,

Stacey Huntsinger

Stacey Huntsinger, RAC
Sr. International Regulatory Associate

Desk copy: R. Rodriguez, Project Manager

CIBA Vision.
A Novartis Company

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

VIA FEDERAL EXPRESS
NDA 21-066

March 17, 1999

Wiley Chambers, M.D., Deputy Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-Inflammatory, Analgesic, and
Ophthalmic Drug Products, HFD-550
Attention: Division Document Room
9201 Corporate Boulevard
Rockville, MD 20850-3202

RE: NDA 21-066 - Ketotifen Fumarate Ophthalmic Solution
NDA Amendment – Preclinical Information

Dear Dr. Chambers:

In response to a request from the Division made by phone today, this amendment provides a missing page from the following study:

HC 20-511 A 13-Week Oral Toxicity Study in Dogs

The information included in this amendment should be forwarded to Dr. Chen. If there are questions or comments regarding this submission, please contact the undersigned at (770) 418- 4343.

Sincerely,

Stacey Huntsinger

Stacey Huntsinger, RAC
Sr. International Regulatory Associate

Desk copy: R. Rodriguez, Project Manager (via fax)

ORIGINAL

VIA FEDERAL EXPRESS
NDA 21-066

NDA ORIG AMENDMENT

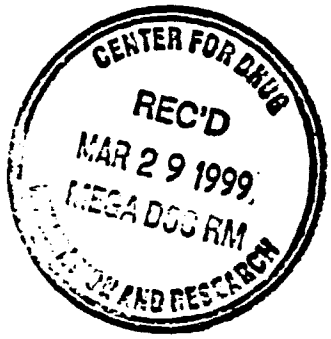
BP

March 25, 1999

CIBA Vision
A Novartis Company

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

Wiley Chambers, M.D., Deputy Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-Inflammatory, Analgesic, and
Ophthalmic Drug Products, HFD-550
Attention: Division Document Room
9201 Corporate Boulevard
Gaithersburg, MD 20850-3202



RE: NDA 21-066 - Ketotifen Fumarate Ophthalmic Solution
NDA Amendment – Response to Preclinical Issues

Dear Dr. Chambers:

In response to several requests for preclinical information made during the pre-NDA meeting, by facsimile and by telephone, please find attached an amendment to the NDA that provides the following information:

REFORMATTED RAW DATA FOR TWO CARCINOGENCITY STUDIES

- Cancerogenic Potential Study in Mice
- Two Years Toxicity Study in Rats

AREA UNDER CURVE CALCULATIONS FOR THREE PHARMACOKINETIC STUDIES

- Plasma levels in rats after acute and chronic oral administration of HC 20-511
- Ketotifen ^{14}C: absorption, blood levels, distribution and excretion in the mouse
- Distribution of ^{14}C ketotifen fumarate in rabbit eye tissue after single and repeated doses of ophthalmic solution

Electronic copies of the requested carcinogenicity raw data are being provided as a part of this amendment. CIBA Vision certifies that the electronic data included on two disks is identical to that provided as a paper copy.

Please note that the area under the curve calculation is outstanding for one additional study: The pharmacokinetics of ^{14}C-HC 20-511 in rat, dog and rhesus monkey. This information will be provided to the Division by April 9, 1999.

If there are questions or comments regarding this amendment, please contact the undersigned at (770) 418- 4343.

Sincerely,

Stacey E. Huntsinger, RAC
Sr. International Regulatory Associate

Desk copy: R. Rodriguez, Project Manager

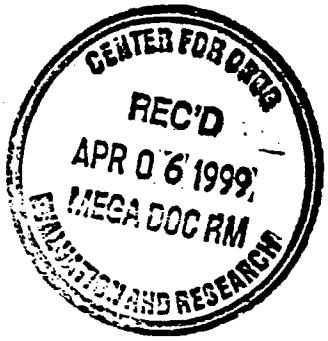
ORIGINAL

VIA FEDERAL EXPRESS
NDA 21-066

ORIG AMENDMENT

April 2, 1999

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



Wiley Chambers, M.D., Deputy Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-Inflammatory, Analgesic, and
Ophthalmic Drug Products, HFD-550
Attention: Division Document Room
9201 Corporate Boulevard
Rockville, MD 20850-3202

RE: NDA 21-066 - Ketotifen Fumarate Ophthalmic Solution
NDA Amendment – Response to Preclinical Issues

Dear Dr. Chambers:

Reference is made to a March 25, 1999 amendment to NDA 21-066 for ketotifen fumarate ophthalmic solution. In that amendment, CIBA Vision provided both reformatted raw data for carcinogenicity studies and area under the curve calculations for several pharmacokinetic studies as requested by the Division. In the cover letter for that amendment, CIBA Vision stated that an area under the curve calculation was outstanding for one additional study.

This amendment provides the area under the curve calculation requested for the additional study:

- Ketotifen (HC 20-511) - The pharmacokinetics of 14C-HC 20-511 in rat, dog and rhesus monkey.

Additionally, CIBA Vision was requested by the preclinical reviewer on 04-02-99 to provide a page missing from the following study:

- HC 20-511 - An eye irritation study in rabbits.

CIBA Vision is providing a copy of the full study report in this amendment for the reviewer's convenience.

During the 04-02-99 conversation between Dr. Chen and S. Huntsinger, it was also requested that the strength of ketotifen fumarate ophthalmic solution used in the following study be clarified:

- Eye Irritation Study in Rabbits after Repeated Doses of Ketotifen Fumarate Eye Drops of Degraded Quality (Volume 7, Reference 56, pages 2156 – 2186).

The concentration of the ketotifen fumarate ophthalmic solution used in that study was 0.05% ketotifen base for the degraded and normal test articles.

If there are questions or comments regarding this amendment, please contact the undersigned at (770) 418- 4343.

Sincerely,

Stacey E. Huntsinger

Stacey E. Huntsinger, RAC
Sr. International Regulatory Associate

Desk copy: R. Rodriguez, Project Manager

VIA FEDERAL EXPRESS
NDA 21-066

Vision.
A Novartis Company

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

April 21, 1999

ORIG AMENDMENT
BP

Wiley Chambers, M.D., Deputy Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-Inflammatory, Analgesic, and
Ophthalmic Drug Products, HFD-550
Attention: Division Document Room
9201 Corporate Boulevard
Rockville, MD 20850-3202

RE: NDA 21-066 - Ketotifen Fumarate Ophthalmic Solution
NDA Amendment – Response to Preclinical Issues

Dear Dr. Chambers:

Reference is made to March 25th and April 2nd amendments to NDA 21-066 for ketotifen fumarate ophthalmic solution. In those amendments, CIBA Vision provided reformatted raw data for carcinogenicity studies and area under the curve calculations for several pharmacokinetic studies as requested by the Division. This amendment provides information requested by the Division to support the March 25th and April 2nd amendments.

This amendment also provides the formulation used for the 13 week toxicity of ketotifen/theophylline 1/300, Lot No. 231 – called for short 'KT 1/300' – by oral administration to beagle dogs (Volume 10, pages 257 – 503). Dr. Chen requested this information on March 18, 1999.

If there are questions or comments regarding this amendment, please contact the undersigned at (770) 418- 4343.

Sincerely,

Stacey E. Huntsinger

Stacey E. Huntsinger, RAC
Sr. International Regulatory Associate

Desk copy: R. Rodriguez, Project Manager

ORIGINAL

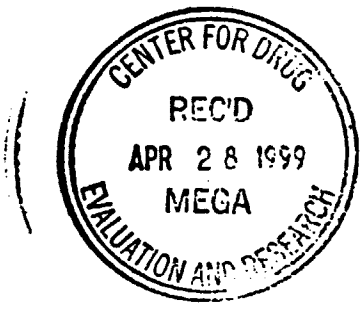
BP

CIBA Vision.
A Novartis Company

VIA FEDERAL EXPRESS
NDA 21-066

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

April 26, 1999



Wiley Chambers, M.D., Deputy Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-Inflammatory, Analgesic, and
Ophthalmic Drug Products, HFD-550
Attention: Division Document Room
9201 Corporate Boulevard
Rockville, MD 20850-3202

RE: NDA 21-066 - Ketotifen Fumarate Ophthalmic Solution
NDA Amendment – Reformatted Carcinogenicity Information

Dear Dr. Chambers:

As requested by FDA in a teleconference on April 7, 1999, this amendment provides reformatted carcinogenicity data for the following study:

- Ketotifen HC 20-511- Two years toxicity study in rats

If there are questions or comments regarding this amendment, please contact the undersigned at (770) 418- 4343.

Sincerely,

Stacey E. Huntsinger

Stacey E. Huntsinger, RAC
Sr. International Regulatory Associate

Desk copy: R. Rodriguez, Project Manager

DUPLICATE

VIA FEDERAL EXPRESS
NDA 21-066

CIBA Vision
A Novartis Company

April 30, 1999

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

Wiley Chambers, M.D., Deputy Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-Inflammatory, Analgesic, and
Ophthalmic Drug Products, HFD-550
Attention: Division Document Room
9201 Corporate Boulevard
Rockville, MD 20850-3202

SU

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
MAY 05 1999
MEGA

RE: NDA 21-066 - Ketotifen Fumarate Ophthalmic Solution
NDA Amendment - 4 Month Safety Update

Dear Dr. Chambers:

In accordance with 21 CFR Section 314.50 (5) (vi) (b), CIBA Vision is submitting a four-month safety update to NDA 21-066 for ketotifen fumarate ophthalmic solution. The original NDA 21-066 was submitted on December 31, 1998. This safety update contains the following information:

- Study synopses for two clinical trials completed following the original NDA submission
- Information on serious adverse events and withdrawals for newly completed clinical trials
- Revised integrated summary of safety
- Preclinical study report of effects of ketotifen on eosinophil infiltration into the guinea pig conjunctiva
- Revised package insert reflecting the changes in the integrated summary of safety

If there are any questions or comments regarding this safety update, please contact the undersigned at (770) 418-4343.

Sincerely,

Stacey E. Huntsinger, RAC
Sr. International Regulatory Associate

Desk copy: R. Rodriguez, Project Manager

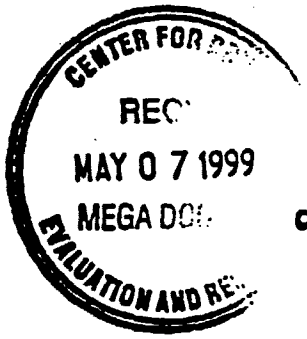
ORIGINAL

CIBA Vision.
A Novartis Company

VIA FEDERAL EXPRESS

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

May 5, 1999



Wiley Chambers, M.D., Deputy Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-Inflammatory, Analgesic, and
Ophthalmic Drug Products, HFD-550
Attention: Division Document Room
9201 Corporate Boulevard
Rockville, MD 20850-3202

RE: NDA 21-066 - Ketotifen Fumarate Ophthalmic Solution
NDA Amendment – Microbiology Information

Dear Dr. Chambers:

In response to microbiology questions forwarded to CIBA Vision on April 20, 1999, this amendment addresses the following:

- Explanation as to disposition and corrective actions for dye ingress failures seen on stability testing
- Summary of antimicrobial preservative effectiveness results for all lots on stability

The Division identified these issues in response to a March 5, 1999 amendment to NDA 21-066 that provided additional microbiological information. The original NDA was filed on December 31, 1998.

If there are questions or comments regarding this amendment, please contact the undersigned at (770) 418-4343.

Sincerely,

Stacey E. Huntsinger

Stacey E. Huntsinger, RAC
Sr. International Regulatory Associate

Desk copy: R. Rodriguez, Project Manager

ORIGINAL

VIA FEDERAL EXPRESS
NDA 21-066

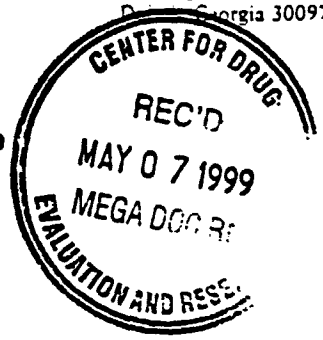
CIBA Vision
A Novartis Company

May 5, 1999

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

Wiley Chambers, M.D., Deputy Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-Inflammatory, Analgesic, and
Ophthalmic Drug Products, HFD-550
Attention: Division Document Room
9201 Corporate Boulevard
Rockville, MD 20850-3202

[redacted]
BC



RE: NDA 21-066 - Ketotifen Fumarate Ophthalmic Solution
NDA Amendment – Stability and General CMC Information

Dear Dr. Chambers:

CIBA Vision is providing the following information as an amendment to NDA 21-066 for ketotifen fumarate ophthalmic solution 0.025%:

- Updated stability data for trade and sample sizes
- Revised certificates of analysis for three finished product batches (osmolality limits have been corrected)
- Certificate of analysis for ketotifen fumarate reference standard

The original NDA for ketotifen fumarate ophthalmic solution was filed on December 31, 1998.

If there are questions or comments regarding this submission, please contact the undersigned at (770) 418- 4343.

Sincerely,

Stacey E Huntsinger

Stacey Huntsinger, RAC
Sr. International Regulatory Associate

Desk copy: R. Rodriguez, Project Manager (via fax)

VIA FEDERAL EXPRESS
NDA 21-066

ORIGINAL

SU
BM

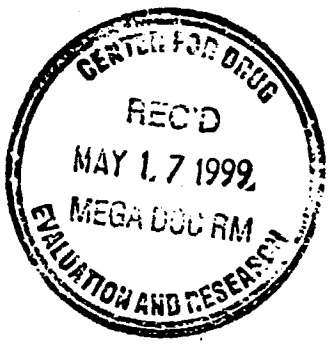
CIBA Vision.
A Novartis Company

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

May 14, 1999

Wiley Chambers, M.D., Deputy Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-Inflammatory, Analgesic, and
Ophthalmic Drug Products, HFD-550
Attention: Division Document Room
9201 Corporate Boulevard
Rockville, MD 20850-3202

DRUG AMENDMENT



RE: NDA 21-066 - Ketotifen Fumarate Ophthalmic Solution
Amendment - Clinical Trial SH/DR 42000-97-2
Southern Hemisphere Environmental Study

Dear Dr. Chambers:

In accordance with a commitment made in the 4 month safety update for NDA 21-066 submitted on April 30, 1999, this amendment the final clinical trial report for the following clinical study:

- Double-masked, Randomized, Parallel Group, Multi-center Comparison of Ophthalmic Ketotifen with its Vehicle and with Levocabastine in Patients Suffering from Seasonal Allergic Conjunctivitis

If there are questions or comments regarding this submission, please contact the undersigned at (770) 418- 4343.

Sincerely,

Stacey E Huntsinger

Stacey Huntsinger, RAC
Sr. International Regulatory Associate

Desk copy: R. Rodriguez, Project Manager

ORIGINAL

VIA FEDERAL EXPRESS
NDA 21-066

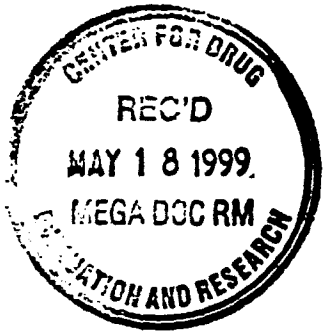
CIBA Vision
A Novartis Company

May 17, 1999

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

ORIG AMENDMENT

Wiley Chambers, M.D., Deputy Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-Inflammatory, Analgesic, and
Ophthalmic Drug Products, HFD-550
Attention: Division Document Room
9201 Corporate Boulevard
Rockville, MD 20850-3202



RE: NDA 21-066 - Ketotifen Fumarate Ophthalmic Solution
Amendment - Clinical Trial UK/DR 42000-98-4

Dear Dr. Chambers:

In accordance with a commitment made in the 4 month safety update for NDA 21-066 submitted on April 30, 1999, this amendment the final clinical trial report for the following clinical study:

- **Double Masked, Randomized, Four-Treatment, Four-Period Cross-Over study to Evaluate the Effect of ketotifen 0.1% and 0.025% Ophthalmic Solutions on Cognitive Performance in Healthy Subjects, Using a Positive and a Placebo Control**

If there are questions or comments regarding this submission, please contact the undersigned at (770) 418- 4343.

Sincerely,

Stacey Huntsinger

Stacey Huntsinger, RAC
Sr. International Regulatory Associate

DUPLICATE

CIBA Vision.
A Novartis Company

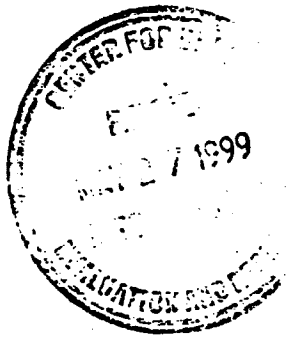
VIA FEDERAL EXPRESS
NDA 21-066

ORIG AMENDMENT

BM

May 18, 1999

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



Wiley Chambers, M.D., Deputy Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-Inflammatory, Analgesic, and
Ophthalmic Drug Products, HFD-550
Attention: Division Document Room
9201 Corporate Boulevard
Rockville, MD 20850-3202

Noted 6/25/99

RE: NDA 21-066 - Ketotifen Fumarate Ophthalmic Solution
Amendment - Clinical Trial SH/DR 42000-97-2
Southern Hemisphere Environmental Study

Dear Dr. Chambers:

In accordance with a commitment made in the 4 month safety update for NDA 21-066 submitted on April 30, 1999, this amendment contains case report forms for all subjects withdrawing (regardless of reason) from the following clinical study:

- Double-masked, Randomized, Parallel Group, Multi-center Comparison of Ophthalmic Ketotifen with its Vehicle and with Levocabastine in Patients Suffering from Seasonal Allergic Conjunctivitis

If there are questions or comments regarding this submission, please contact the undersigned at (770) 418- 4343.

Sincerely,

Stacey Huntsinger

Stacey Huntsinger, RAC
Sr. International Regulatory Associate

DUPLICATE

BP

VIA FEDERAL EXPRESS

CIBA Vision.
A Novartis Company

May 24, 1999

ORIG AMENDMENT

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

Wiley Chambers, M.D., Deputy Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-Inflammatory, Analgesic, and
Ophthalmic Drug Products, HFD-550
Attention: Division Document Room
9201 Corporate Boulevard
Rockville, MD 20850-3202

RE: NDA 21-066 - Ketotifen Fumarate Ophthalmic Solution
NDA Amendment – Preclinical information

Dear Dr. Chambers:

As FDA requested by telephone on May 12, 1999 and May 18, 1999, this amendment provides additional information regarding the following preclinical studies originally submitted in [redacted] for ketotifen fumarate ophthalmic solution:

- HC 20-511 - A teratological study in rabbits
- HC 20-511 – A teratological study in rats

Also provided in this amendment is a comparison of the formulation used in three ocular toxicology studies which supported the Japanese registration of ketotifen fumarate ophthalmic solution 0.05% and the formulation [redacted]

This information should be provided to Dr. Chen, preclinical reviewer. [redacted]

If there are questions or comments regarding this amendment, please contact the undersigned at (770) 418- 4343.

Sincerely,

Stacey E. Huntsinger

Stacey E. Huntsinger, RAC
Sr. International Regulatory Associate

Desk copy: R. Rodriguez, Project Manager (via fax)

ORIGINAL

VIA FEDERAL EXPRESS

CIBA Vision
A Novartis Company

June 4, 1999

DRUG AMENDMENT

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

Wiley Chambers, M.D., Deputy Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-Inflammatory, Analgesic, and
Ophthalmic Drug Products, HFD-550
Attention: Division Document Room
9201 Corporate Boulevard
Rockville, MD 20850-3202

BP

Noted 6/16/99

CENTER FOR DRUG EVALUATION
RECD
JUN 0 8 1999
MEDICINE

RE: NDA 21-066 - Ketotifen Fumarate Ophthalmic Solution
NDA Amendment – Preclinical information

Dear Dr. Chambers:

As FDA requested by telephone on May 18, 1999, May 19, 1999 and June 3, 1999, this amendment provides additional information regarding the following preclinical studies originally submitted in [redacted] for ketotifen fumarate ophthalmic solution:

- Fertility Study in Female Rats
- Peri- and Postnatal Study in Rats
- HC 20-511 - A teratological study in rabbits
- HC20-511 – A teratological study in rats

This information should be provided to Dr. Chen, preclinical reviewer. [redacted]

If there are questions or comments regarding this amendment, please contact the undersigned at (770) 418- 4343.

Sincerely,

Stacey E Huntsinger

Stacey E. Huntsinger, RAC
Sr. International Regulatory Associate

Desk copy: R. Rodriguez, Project Manager (via fax)

ORIGINAL

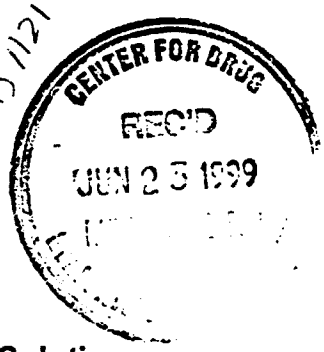
VIA FEDERAL EXPRESS

CIBA Vision
A Novartis Company

June 21, 1999

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

Wiley Chambers, M.D., Deputy Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-Inflammatory, Analgesic, and
Ophthalmic Drug Products, HFD-550
Attention: Division Document Room
9201 Corporate Boulevard
Rockville, MD 20850-3202



RE: NDA 21-066 - Ketotifen Fumarate Ophthalmic Solution
NDA Amendment – Response to Issues from

Dear Dr. Chambers:

In response to a facsimile dated June 3, 1999 raising issues affecting the approval status of NDA 21-066 for ketotifen fumarate ophthalmic solution 0.025%, CIBA Vision is submitting the following amendment.

This amendment addresses the seven "approvability" issues raised in the June 3, 1999 facsimile and includes the following information:

- Commitment and timeline for providing systemic absorption data after ophthalmic administration of ketotifen
- Revisions to container and carton labeling, package insert
- Additional stability data to support 18 month expiration date
- Revisions to stability protocols and stability commitment
- Revisions to manufacturing batch record
- Deletion of "fall back" testing in the event that chemical testing for benzalkonium chloride is out of specifications
- Revisions to release and regulatory specifications for related substances in the finished product

CIBA Vision is working to address the remaining concerns (numbered 8 – 51) related to chemistry, manufacturing and controls that were raised in the facsimile of June 3, 1999, but were not required for approval of NDA 21-066. Timelines for responding will be provided by mid-July.

CIBA Vision believes that the key issues affecting the approval status of NDA 21-066 are addressed with this amendment. If there are questions or comments regarding this submission, please contact the undersigned at (770) 418- 4343.

Sincerely,

Stacey E Huntsinger

Stacey Huntsinger, RAC
Sr. International Regulatory Associate

APPEARS THIS WAY
ON ORIGINAL

CIBA Vision
A Novartis Company

VIA FEDERAL EXPRESS
NDA 21-066

June 30, 1999

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

Wiley Chambers, M.D., Deputy Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-Inflammatory, Analgesic, and
Ophthalmic Drug Products, HFD-550
Attention: Division Document Room
9201 Corporate Boulevard
Rockville, MD 20850-3202

RE: NDA 21-066: ZADITOR™
Ketotifen fumarate ophthalmic solution 0.025%
Amendment – Response to issues raised on 06-28-99 and 06-29-99

Dear Dr. Chambers:

Please find attached an amendment which addresses the following issues raised by the Division in facsimiles dated 06-28-99 and 06-29-99 and discussed in today's teleconference. The information provided includes:

- Response to request for revision of appearance and colour of solution specifications for ketotifen fumarate
- Acceptance of proposed specifications for related substances in the finished product
- Requested information regarding corrective actions taken to address tip placement and cap sealing during packaging
- Acknowledgement that FDA review of carcinogenicity data is on-going
- Revised package insert with commitment to revise container labels and cartons

If there are questions or comments regarding this amendment, please contact the undersigned at (770) 418-4343.

Sincerely,

Stacey E. Huntsinger

Stacey E. Huntsinger, RAC
Sr. International Regulatory Associate

Cc: R. Rodriguez, Project Manager

VIA FACSIMILE
NDA 21-066

CIBA Vision.
A Novartis Company

July 1, 1999

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

Wiley Chambers, M.D., Deputy Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-Inflammatory, Analgesic, and
Ophthalmic Drug Products, HFD-550
Attention: Division Document Room
9201 Corporate Boulevard
Rockville, MD 20850-3202

RE: NDA 21-066: ZADITOR™
Ketotifen fumarate ophthalmic solution 0.025%
Amendment – Response to issues raised on 07-01-99

Dear Dr. Chambers:

Please find attached an amendment that addresses the following issues raised by the Dr. Eng and Dr. Fenslow in a telephone call earlier this afternoon. The following information is being provided:

- Acceptance of proposed specifications for related substances in the finished product (with 2.0% as total related substances specification)
- Full copy of SOP 30-1003-05 (previous fax was missing pages)
- Copies of the current on-line monitoring form and the obsolete form for comparison

If there are questions or comments regarding this amendment, please contact the undersigned at (770) 418-4343.

Sincerely,

Stacey E. Huntsinger

Stacey E. Huntsinger, RAC
Sr. International Regulatory Associate

Cc: R. Rodriguez, Project Manager

CIBA Vision.
A Novartis Company

VIA FACSIMILE
NDA 21-066

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

July 1, 1999

Wiley Chambers, M.D., Deputy Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-Inflammatory, Analgesic, and
Ophthalmic Drug Products, HFD-550
Attention: Division Document Room
9201 Corporate Boulevard
Rockville, MD 20850-3202

RE: NDA 21-066: ZADITOR™
Ketotifen fumarate ophthalmic solution 0.025%
Acceptance of labeling

Dear Dr. Chambers:

CIBA Vision accepts the labeling as proposed by the Division in a facsimile dated July 1, 1999. A copy of this labeling is attached for reference.

If there are questions or comments regarding this correspondence, please contact the undersigned at (770) 418-4343.

Sincerely,

Stacey E. Huntsinger

Stacey E. Huntsinger, RAC
Sr. International Regulatory Associate

Cc: R. Rodriguez