CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: **21-066**

CHEMISTRY REVIEW(S)

Division of Anti-inflammatory, Analgesic and Ophthalmic Drugs
Review of Chemistry, Manufacturing, and Controls

NDA #: 21-066

REVIEW # 1 **DATE REVIEWED:** 25-MAY-99

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
SUBMISSION	31-DEC-98	04-JAN-99	06-JAN-99
AMENDMENT	03-FEB-99	04-FEB-99	10-FEB-99
	26-FEB-99	01-MAR-99	04-MAR-99
	05-MAY-99	07-MAY-99	11-MAY-99

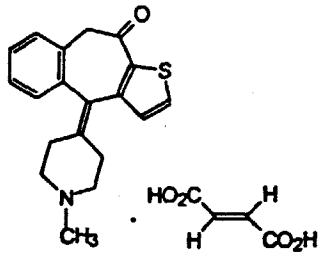
NAME & ADDRESS OF APPLICANT: CIBA Vision Corporation
11460 Johns Creek Parkway
Duluth, GA 30097-1556

DRUG PRODUCT NAME:
Proprietary:
Established: Ketotifen Fumarate
Code Name/#: 34580-14-8
Chem.Type/Ther.Class: P/

PHARMACOL. CATEGORY: Anti-anaphylactic and antihistaminic H1-receptor antagonist

DOSAGE FORM: Ophthalmic Solution
STRENGTHS: 0.025% (w/v)
ROUTE OF ADMINISTRATION: Topical (ocular)
DISPENSED: _X_ Rx __ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA AND WEIGHT:



$C_{19}H_{19}NOS \cdot C_4H_4O_4$
M.W.: 425.50

9,10-Dihydro-4-(1-methyl-4-piperidylidene)-10-oxo-4*H*-benzo[4,5]cyclohepta[1,2-*b*]thiophene fumarate

KETOTIFEN FUMARATE

REMARKS:

Drug Substance: A number of substantive issues on various aspects of drug substance manufacture and testing have been identified, relating to structure determination, sourcing of starting material, conditions for international shipping and acceptance testing of a critical synthetic intermediate, details of test procedure for quantitating impurities in drug substance, and the apparent instability of material manufactured at the [redacted] (along with other questions of lesser substance).

Drug Product: Varied and numerous problems have been identified that impact on assurance of product quality and safety. The sample batch record contains omissions and lacks precise details to insure batch-to-batch uniformity. The test procedure for determining the content of the active substance is not a dedicated procedure, but is a general purpose assay for the substance even in cleaning validation samples. Major manufacturing problems with the most recent and largest product batches manufactured to date (which is still only [redacted] of the scale proposed for the commercial batches) have been uncovered which are associated with the container/closure system integrity. No information is presented on the exact cause(s) of these problems, the specific corrective actions taken, and the effectiveness of these changes in eliminating these problems. The proposed final product regulatory specifications permit levels of related substances that are not justifiable based on the stability study results. The product stability is such that an expiry period cannot be determined from the limited data available at this time; in addition, the data have been obtained with suspect product batches (from the manufacturing problems). The stability data also suggest that significant amounts of undetected related substances accumulate during storage. The manufacturing problems require examination of product sterility during storage; no stability samples have been subjected to the complete testing regimen, which means questions about sterility and preservative effectiveness are yet to be answered. In addition to these concerns, a sizeable number of questions need to be addressed on all aspects of drug product manufacture and testing.

CONCLUSIONS & RECOMMENDATIONS:

The number and seriousness of the problems associated with the manufacture and testing of drug substance and drug product require a thorough response by the applicant before approval can be recommended. At this time, the submission is evaluated as APPROVABLE. Please see the chemist's draft letter for details.

cc:
Orig. NDA 21-066
HFD-550/Division File
HFD-550/CHEM/A.Fenselau
HFD-550/CSO/R.Rodriguez

/S/ 5/26/99
Allan Fenselau, Review Chemist, HFD-550

/S/ 6/1/99
Linda Ng, Chemistry Team Leader HFD-550

[redacted]

Division of Anti-inflammatory, Analgesic and Ophthalmic Drugs
Review of Chemistry, Manufacturing, and Controls

NDA #: 21-066

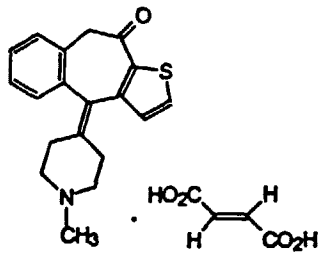
REVIEW # 2 **DATE REVIEWED:** 30-JUN-99

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
SUBMISSION	31-DEC-98	04-JAN-99	06-JAN-99
PREVIOUS	03-FEB-99	04-FEB-99	10-FEB-99
AMENDMENTS:	26-FEB-99	01-MAR-99	04-MAR-99
	05-MAY-99	07-MAY-99	11-MAY-99
AMENDMENT UNDER REVIEW:	21-JUN-99	23-JUN-99	21-JUN-99

NAME & ADDRESS OF APPLICANT: CIBA Vision Corporation
11460 Johns Creek Parkway
Duluth, GA 30097-1556

DRUG PRODUCT NAME:
- Proprietary: ZADITOR™
- Established: Ketotifen Fumarate
- Code Name/#: 34580-14-8
- Chem.Type/Ther.Class: P/

PHARMACOL. CATEGORY: Anti-anaphylactic and antihistaminic H1-receptor antagonist
DOSAGE FORM: Ophthalmic Solution
STRENGTHS: 0.025% (w/v)
ROUTE OF ADMINISTRATION: Topical (ocular)
DISPENSED: 1 drop/eye every 8-12 hr X Rx __ OTC
CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA AND WEIGHT:



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9,10-Dihydro-4-(1-methyl-4-piperidylidene)-10-oxo-4*H*-benzo[4,5]cyclohepta[1,2-*b*]thiophene fumarate

KETOTIFEN FUMARATE

REMARKS:
Drug Substance: The concern about the apparent instability and impurity of material manufactured at the [redacted] site can be alleviated by the applicant's revision of the drug substance specifications. Their intention to describe ketotifen fumarate in the Package Insert as a "white" powder requires revision of the specifications to state the drug substance Appearance as "White" and its Colour of the solution as "Not more intensely coloured than faintly yellow." Agreement to make these changes has not been received as of 30-JUN-99.

Drug Product: Varied and numerous problems that impact on assurance of product quality and safety were identified by Review #1. The sample batch record contained omissions and lacks precise details to insure batch-to-batch uniformity. The batch record submitted on 21-JUN-99 is acceptable as far as it goes, which is through the formulation process. No instructions on product fill and packaging were included in this document. Since major manufacturing problems are associated with the container/closure system integrity of the most recent and largest product batches manufactured to date, more documentation is needed to assure that these problems will not re-occur. To date, no information has been presented on the exact cause(s) of these problems, the specific corrective actions taken, and the effectiveness of these changes in eliminating these problems. An evaluation of these matters from the facility inspection is unavailable at this time. The revised final product regulatory specifications permit levels of related substances that still are not justifiable based on the stability study results and an expiry period of 18 months. A further modification that narrows the acceptable range for these substances has been proposed. The product stability data now extend to a minimum of 12 months and are consistent with the use of an 18 month expiration of the drug product. However, to provide greater assurance of product safety, the applicant has agreed to perform full product testing at each time station [which now includes sterility, container closure integrity [redacted] and particulate matter testing] and has committed to withdraw from the market drug product which fails to meet specifications. In addition to these concerns, a sizeable number of questions still need to be addressed on all aspects of drug product manufacture and testing. For example, the test procedure for determining the content of the active substance is not a dedicated procedure, but is a general purpose assay for the substance even in cleaning validation samples. Nevertheless, if the revised specifications for the drug product are acceptable to the applicant and the issue of manufacturing problems has been satisfactorily addressed, approval of the drug product can be given.

CONCLUSIONS & RECOMMENDATIONS:

If the applicant agrees to the proposed revisions to the specifications for drug substance and drug product and if the inspection confirms that the manufacturing changes at the Mississauga, Canada site will correct the serious problems in tip placement and container closure, the submission can be APPROVED. Please see the chemist's draft letter for details.

cc:
Orig. NDA 21-066
HFD-550/Division File
HFD-550/CHEM/A.Fenselau
HFD-550/CSO/R.Rodriguez

/S/ 6/30/99
Allan Fenselau, Review Chemist, HFD-550

/S/ 6/30/99
Linda Ng, Chemistry Team Leader HFD-550

[redacted]

Division of Anti-inflammatory, Analgesic and Ophthalmic Drugs
Review of Chemistry, Manufacturing, and Controls

NDA #: 21-066

REVIEW # 3 **DATE REVIEWED:** 01-JUL-99

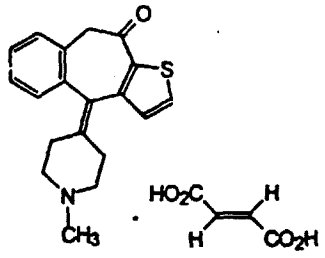
SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
SUBMISSION	31-DEC-98	04-JAN-99	06-JAN-99
PREVIOUS	03-FEB-99	04-FEB-99	10-FEB-99
AMENDMENTS:	26-FEB-99	01-MAR-99	04-MAR-99
	05-MAY-99	07-MAY-99	11-MAY-99
	21-JUN-99	23-JUN-99	21-JUN-99
AMENDMENTS UNDER REVIEW:	30-JUN-99	02-JUL-99	01-JUL-99
	01-JUL-99	02-JUL-99	01-JUL-99

NAME & ADDRESS OF APPLICANT: CIBA Vision Corporation
11460 Johns Creek Parkway
Duluth, GA 30097-1556

DRUG PRODUCT NAME:
- Proprietary: ZADITOR™
- Established: Ketotifen Fumarate
- Code Name/#: 34580-14-8
- Chem.Type/Ther.Class: P/

PHARMACOL. CATEGORY: Anti-anaphylactic and antihistaminic H1-receptor antagonist
DOSAGE FORM: Ophthalmic Solution
STRENGTHS: 0.025% (w/v)
ROUTE OF ADMINISTRATION: Topical (ocular)
DISPENSED: 1 drop/eye every 8-12 hr _X_ **Rx** __ **OTC**

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA AND WEIGHT:



KETOTIFEN FUMARATE

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M.W.: 425.50

9,10-Dihydro-4-(1-methyl-4-piperidylidene)-10-oxo-4*H*-benzo[4,5]cyclohepta[1,2-*b*]thiophene fumarate

REMARKS:

Drug Substance: The concern about the apparent instability and impurity of material manufactured at the [redacted] site will be addressed by studies on 1) the origin and variability of appearance for batches manufactured at [redacted] and 2) the shift in results for color of solution testing (as seen on stability at [redacted]). The results will be provided by 31-DEC-99. The term "white" will be removed from the description of ketotifen fumarate in the Package Insert. The drug substance specifications for Appearance and Colour of the solution may require revision based on the findings.

Drug Product: Several problems that impact on assurance of product quality and safety still remained after Review #2. Complete and completed batch records for lots 80737 (physician sample size) and 80749 (commercial size) have been submitted and are acceptable. The issue of the major manufacturing problems associated with the container/closure system integrity has been adequately addressed by a) revision of two critical SOPs [on 1) defect classification and quality assurance monitor of ophthalmic production and 2) monitoring of filling operation torque checks] and b) a revised and more stringent on-line monitor form attached to the batch record. In addition, findings from a study that examined container closure integrity with non-commercial product lots manufactured using the revised procedures indicated that no samples failed the [redacted] testing. The revised final product regulatory specifications for the specified and unspecified individual and total related substances have been agreed upon by the applicant. Print size relationships for the established and proprietary names on the product labels and cartons will also be followed in accord with 21 CFR 201.10(g)(2). Other concerns identified in the 03-JUN-99 draft letter to the applicant have yet to be fully addressed, but the various revisions and commitments that have been made to date by the applicant assure the manufacture of a safe product.

CONCLUSIONS & RECOMMENDATIONS:

The applicant agrees to the proposed revisions to the specifications for drug product and commits to studying the anomalies in the manufacture of the drug substance (and to submit a completed report by 31-DEC-99). Review of the documentation on the corrective actions taken by CIBA Vision concerning their manufacturing problems and an acceptable inspection at the Mississauga, Canada site remove the last of the concerns about the safe manufacture of the drug product. Thus, based on a review of chemistry, manufacturing and controls issues approval can be given to this request to manufacture ZADITOL™ (ketotifen fumarate ophthalmic solution) 0.025%.

/S/ 7/2/99

Allan Fenselau, Review Chemist, HFD-550

/S/ 7/2/99

Linda Ng, Chemistry Team Leader HFD-550

cc:
Orig. NDA 21-066
HFD-550/Division File
HFD-550/CSO/R.Rodriguez
HFD-550/CHEM/A.Fenselau
HFD-550/CHEM/TmLdr/L.Ng
HFD-550/MO/J.Dunbar
HFD-550/DepDivDir/W.Chambers
HFD-830/DNDCIII Div.Dir/C.-w.Chen

[redacted]