CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 77-200

Name: Ketotifen fumarate ophthalmic solution, 0.025%

Sponsor: Alcon Research, Inc.

Approval Date: September 2, 2008

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 77-200

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 77-200

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 77-200

Alcon Research Ltd.
U.S. Agent for: Alcon, Inc.
Attention: Sarah Cantrell
Assistant Director, Regulatory Affairs
6201 South Freeway
Fort Worth, TX 76134-0450

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA) dated July 1, 2004, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Ketotifen Fumarate Ophthalmic Solution, 0.025% (base).

Reference is also made to the tentative approval letter issued by this office on March 17, 2006, and to your amendments dated February 28, 2006, and March 24, April 7, June 11, (two amendments), July 8, July 25, and August 14, 2008.

We have completed the review of this ANDA and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for Over-the-Counter (OTC) use as recommended in the submitted labeling. Accordingly the ANDA is approved, effective on the date of this letter. The Division of Bioequivalence has determined your Ketotifen Fumarate Ophthalmic Solution, 0.025% (base) to be bioequivalent to the reference listed drug, Zaditor Ophthalmic Solution, 0.025% (base) of Novartis Pharmaceuticals Corporation.

Under section 506A of the Act, certain changes in the conditions described in this ANDA require an approved supplemental application before the change may be made.

Postmarketing reporting requirements for this ANDA are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

Sincerely yours,

{See appended electronic signature page}

Gary Buehler
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Robert L. West
9/2/2008 10:08:29 AM
Deputy Director, for Gary Buehler

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 77-200

TENTATIVE APPROVAL LETTER

ANDA 77-200

MAR 17 2006

Alcon Research, Ltd.
Attention: Norma Schafer
US Agent for: Alcon, Inc.
6201 South Freeway
Fort Worth, TX 76134

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA) dated July 1, 2004, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Ketotifen Fumarate Ophthalmic Solution, 0.025%.

Reference is also made to your amendments dated April 7, and October 26, 2005 and February 24, 2006.

We have completed the review of this abbreviated application, and based upon the information you have presented to date we have concluded that the drug is safe and effective for use as recommended in the submitted labeling. However, we are unable to grant final approval to your application at this time because of the patent issue noted below. Therefore, the application is **tentatively approved.** This determination is based upon information available to the Agency at this time, (i.e., information in your application and the status of current good manufacturing practices (cGMPs) of the facilities used in the manufacturing and testing of the drug product). This determination is subject to change on the basis of new information that may come to our attention.

The reference listed drug product (RLD) upon which you have based your application, Zaditor® Ophthalmic Solution, 0.025% of Novartis is subject to multiple periods of patent protection.

The following patents with their expiration dates are currently listed in the Agency's publication titled Approved Drug Products with Therapeutic Equivalence Evaluations, (the "Orange Book"):

U.S Patent Number	Expiration Date
6,774,137(the '137 patent)	January 13, 2019
6,776,982(the '982 patent)	January 13, 2019
6,777,429(the '429 patent)	January 13, 2019

Your application contains paragraph III certifications to the '137, '982,and '429 patents under Section 505(j)(2)(A)(vii)(III) of the Act. These certifications state that Alcon Research, Ltd. will not market this Ketotifen Fumarate Ophthalmic Solution, prior to the expiration of the '137, '982, and '429 patents. Therefore, final approval of your application may not be made effective pursuant to 21 U.S.C. 355(j)(5)(B)(ii) of the Act until the '137, '982, and '429 patents have expired, i.e., January 13, 2019.

In order to reactivate your application prior to final approval, please submit a "MINOR AMENDMENT - FINAL APPROVAL REQUESTED" 90 days prior to the date you believe that your application will be eligible for final approval. This amendment should provide the legal/regulatory basis for your request for final approval, and it should also identify changes, if any, in the conditions under which the product was tentatively approved, i.e., updated information such as final-printed labeling, chemistry, manufacturing, and controls data as appropriate. This amendment should be submitted even if none of these changes were made. This amendment should be designated clearly in your cover letter as a "MINOR AMENDMENT - FINAL APPROVAL REQUESTED".

In addition to the amendment requested above, the Agency may request at any time prior to the date of final approval that you submit an additional amendment containing the requested information. Failure to submit either or, if requested, both amendments may result in rescission of the tentative approval status of your application, or may result in a delay in the issuance of the final approval letter.

Any significant changes in the conditions outlined in this abbreviated application as well as changes in the status of the manufacturing and testing facilities' compliance with current good manufacturing practices (CGMPs) are subject to Agency review before final approval of the application will be made.

Such changes should be submitted as an amendment to the ANDA and categorized as representing either "major" or "minor" changes. The amendment will be reviewed according to OGD policy in effect at the time of receipt. Your submission of multiple amendments prior to final approval may also lead to a delay in the issuance of the final approval letter.

Please note that this drug product may not be marketed without final Agency approval under Section 505 of the Act. The introduction or delivery for introduction into interstate commerce of this drug product before the final approval date is prohibited under Section 501 of the Act and 21 U.S.C. 331(d). Also, until the Agency issues the final approval letter, this drug product will not be deemed approved for marketing under 21 U.S.C. 355 and will not be listed in the Orange Book. Should you believe that there are grounds for issuing the final approval letter prior to January 13, 2019, you should amend your application accordingly.

For further information on the status of this application or upon submitting an amendment to the application, please contact Rosalyn Adigun, Project Manager, at 301-827-5754.

Sincerely yours,

Gary Buehler 3/17/06
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 77-200
Division File
Field Copy
HFD-610/R. West
HFD-205
HFD-610/Orange Book Staff

Endorsements:
HFD-629/L.Huang/
HFD-623/J.Fan/
HFD-617/R.Adigun/
HFD-613/B.Weitzman/
HFD-613/J.Grace/

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F/T by

TENTATIVE APPROVAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 77-200

LABELING

Current Label	Proposed Label
[redacted] (b) (4)	

Annotations
Please find enclosed the following changes: 1) Removal of "Inactive" ingredients listing, 2) Movement of "Dosage" statement, 3) Removal of "Storage" statement, 4) Removal of "Company" information, 5) Enlargement of type size.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 77-200

LABELING REVIEWS

This labeling approval summary supersedes the labeling approval summary dated 4/7/05

APPROVAL SUMMARY #2
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number:	77-200
Date of Submission:	**June 11, 2008 and March 24, 2008**
Applicant's Name:	Alcon, Inc.
Established Name:	Ketotifen Fumarate Ophthalmic Solution USP, 0.025% (OTC)

APPROVAL SUMMARY

CONTAINER LABELS: (5 mL) –

Satisfactory in FPL as of the June 11, 2008 e-submission.

CARTON LABELING:

Satisfactory in FPL as of the June 11, 2008 e-submission.

REFERENCE LISTED DRUG:

- Was this approval based upon a petition? No
- What is the RLD on the 356(h) form: Zaditor® Ophthalmic Solution,
- NDA Number: 21-066
- NDA Drug Name: Ketotifen Fumarate Ophthalmic Solution USP, 0.025%
- NDA Firm: Novartis
- Date of Approval of NDA Insert: NDA 21-066/S011: Approved October 19, 2006
- Has this been verified by the MIS system for the NDA? Yes
- Was this approval based upon an OGD labeling guidance? No
- Basis of Approval for the Container Labels: Side-by-side comparison
- Basis of Approval for the Carton Labels: Side-by-side comparison
- Revisions needed post-approval:

PATENTS/EXCLUSIVITIES-NDA 21-066
There are no unexpired patents or exclusivities for this product.

FOR THE RECORD:

1. **MODEL LABELING**
This review was based on the labeling for Zaditor® (OTC) by Novartis (NDA 21-066/S011: Approved October 19, 2006).

2. **INACTIVE INGREDIENTS**
There does not appear to be a discrepancy in inactives between the DESCRIPTION and the composition statement.

Inactive ingredients
Glycerin
Benzalkonium Chloride
(b) (4) Sodium Chloride
(b) (4) Diluted Hydrochloric Acid
Purified Water

Drug Product Formulation Comparison			
ZADITOR® Ophthalmic Solution (Novartis Ophthalmics)		Ketotifen Fumarate Ophthalmic Solution, 0.025% (Apotex Inc.)	
Qualitative	Quantitative (g per Litre)	Qualitative	Quantitative (g per Litre)
Benzalkonium Chloride	0.1	Benzalkonium Chloride (b) (4))	0.1
Glycerin	(b) (4)	Glycerin USP	(b) (4)
Hydrochloric Acid		Hydrochloric Acid NF/EP	
Ketotifen Fumarate		Ketotifen Fumarate	
Sodium Hydroxide		Sodium Hydroxide NF/EP	
(b) (4)	Present	(b) (4)	

3. **PATENTS/EXCLUSIVITIES-NDA 21-066**
See above.

4. **STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON**
- USP: NONE
- RLD: Stored at 4 - 25°C (39 - 77°F)
- ANDA: Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].

5. **DISPENSING STATEMENT COMPARISON**
- USP: None.
- RLD: None.
- ANDA: None.

6. **PACKAGE CONFIGURATION**
- RLD: Supplied as 5 mL solution in white 7.5 mL LDPE plastic bottles with controlled plastic dropper tip and white plastic caps.
- ANDA: Supplied as 5 mL solution in white 7.5 mL LDPE plastic bottles with controlled plastic dropper tip and white plastic caps.

7. **CONTAINER/CLOSURE**

Packaging component	Description
Bottle	(b) (4)
Plug	
closure	

8. **FINISHED DOSAGE FORM**
- RLD: Supplied as a 1 mL and 5 mL Solution
- ANDA: A clear, colorless solution with strength of 0.025% supplied as a 5 mL solution.

9. **CAP COLOR**
- RLD: White color cap
- ANDA White color cap - Please note that there is no AAO recommended color coding of caps for the class of histamine antagonist. Therefore the default color white is used.

10. **MANUFACTURING FACILITY OF FINISHED DOSAGE FORM**
Alcon Manufacturing Ltd.
ASPEX Manufacturing facilities
6201 South Freeway
Fort Worth, TX 76-134-2099

Date of Review: June 19, 2008

Dates of Submission: **June 11, 2008** and **March 24, 2008**

Primary Reviewer: Postelle Birch-Smith

Team Leader: John Grace

____ANDA: 77-200
DUP/DIVISION FILE

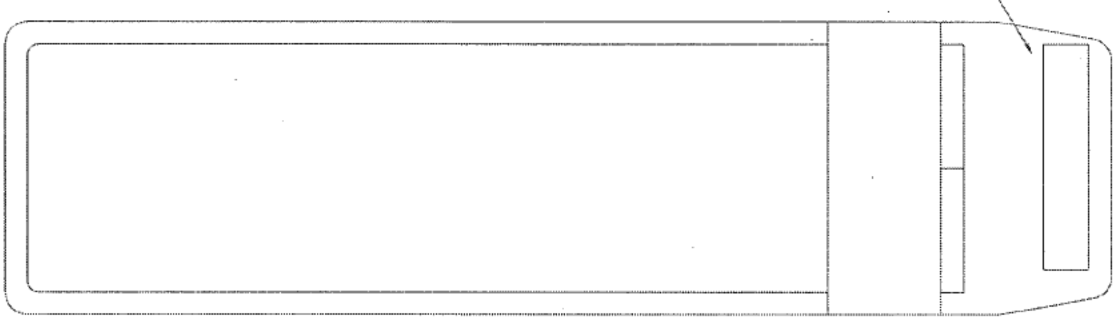
(b) (4)

[redacted]

1. TEXT, COLOR & COATING AREA.
2. COLOR & COATING AREA, NO TEXT ALLOWED.
3. DWG. NO. & CONTROL DATE LOCATION.
4. QUIET AREA - NO TEXT, COLOR OR COATING ALLOWED, EXCEPT AS INDICATED.
5. PREPRINTED "LOT:" LOCATION.
6. PREPRINTED "EXP.:" LOCATION.

DRAWING NUMBER AND CONTROL DATE TO BE UNDERLINED. SEE SPECIFICATION FOR DETAILS.

A00858-C



SCALE: 2X

IXXIXXXXFPOXXXXXXX

SCALE: 1X

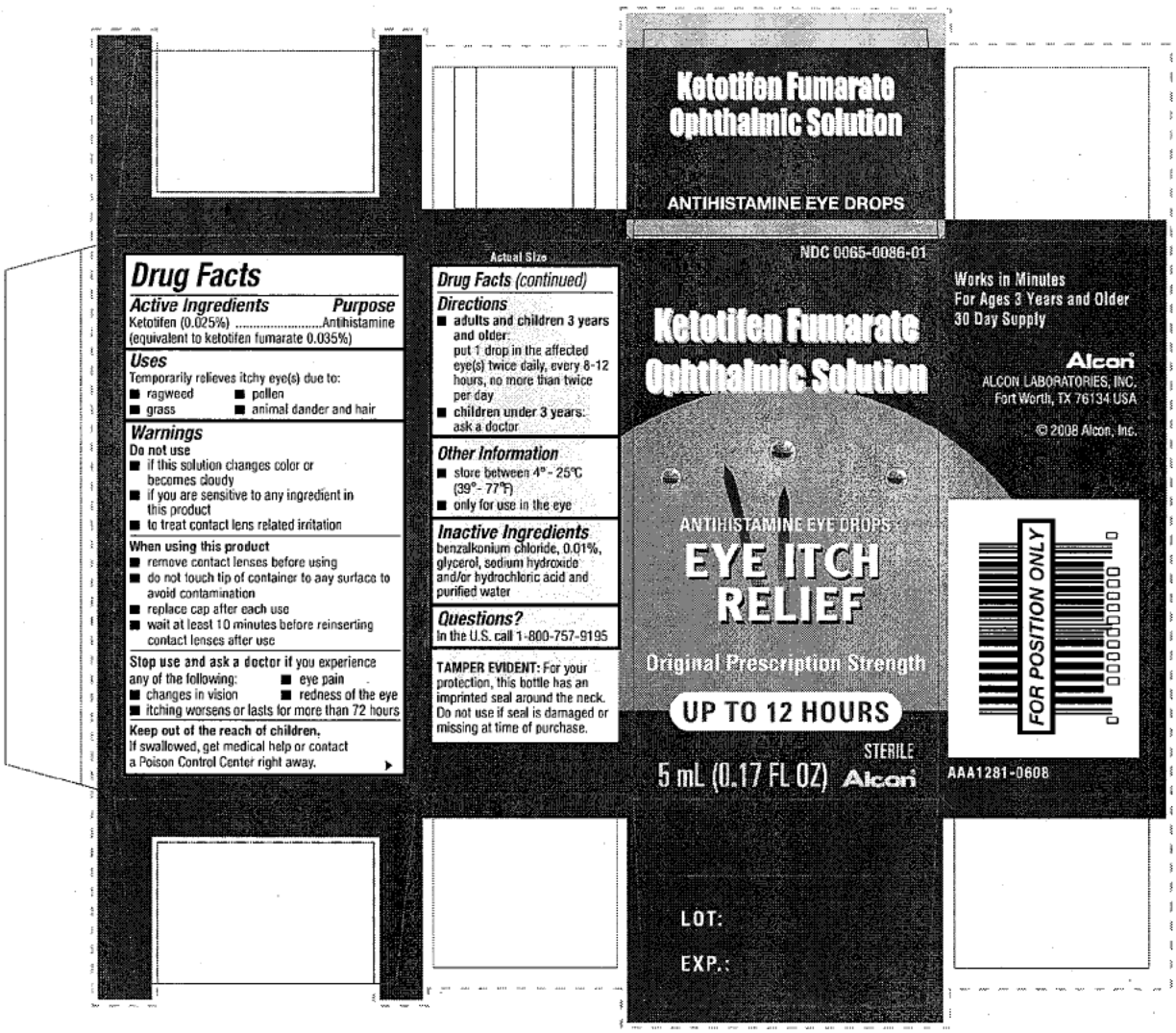
(b) (4)

[redacted]

(b) (4)

1. GLUE AREA - NO TEXT, COLOR OR COATING.
2. CODE AREA - NO TEXT OTHER THAN LOT & EXPIRES. COATING AND COLOR ARE ACCEPTABLE.
3. BAR CODE AREA - FINISHED CODE TO BE CENTERED LEFT TO RIGHT.
4. QUIET AREA - NO TEXT OR COLOR ALLOWED..
5. PREPRINTED "LOT:" LOCATION.
6. PREPRINTED "EXP.:" LOCATION.

GRAPHICS TOP



FRONT

(b) (4)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Postelle Birch
6/20/2008 09:10:36 AM
LABELING REVIEWER

John Grace
6/24/2008 01:13:36 PM
LABELING REVIEWER

REVIEW OF PROFESSIONAL LABELING - #1
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 77-200

Date of Submission: July 1, 2004

Applicant's Name: Alcon Laboratories, Inc.

Established Name: Ketotifen Fumarate Ophthalmic Solution USP, 0.025%

Labeling Deficiencies:

1) **GENERAL COMMENT:** Your Patent Certification is no longer accurate. Please submit an updated Patent Certification Statement. We refer you to the "Approved Drug Products with Therapeutic Equivalence Evaluations" (Orange Book) edition or cumulative supplement for verification of the latest patent.

2) **CONTAINER – 5 mL**

Your container label is difficult to read. Increase the information presented on your label clearly and prominently. Refer to 21 CFR 201.10 (i) for the requirements for a drug packaged in a small container. In addition, you may omit the following information:

"Inactive ingredients"

"Storage temperature"

"The address of the manufacturer for and by"

3) **CARTON - 5 mL** – Satisfactory in Final Printed Labeling.

4) **INSERT** – Satisfactory in Final Printed Labeling.

Please revise your container label, as instructed above, and submit in final print.

The electronic labeling rule published December 11, 2003, (68 FR 69009) requires submission of labeling content in electronic format effective June 8, 2004. For additional information, consult the following guidance for industry regarding electronic submissions: Providing Regulatory Submissions in Electronic Format — ANDAs (Issued 6/2002) (http://www.fda.gov/cder/guidance/5004fnl.htm). The guidance specifies labeling to be submitted in pdf format. To assist in our review, we request that labeling also be submitted in MS Word format.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference-listed drug. In order to keep your ANDA current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address –

http://www.fda.gov/cder/cdernew/listserv.html

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

John J Grunfogel

Wm Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23		X	
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?			X
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?		X	
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?			X
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Labeling(continued)	Yes	No	N.A.
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)			X
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?			X
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
			X

Is the scoring configuration different than the RLD?			
Has the firm failed to describe the scoring in the HOW SUPPLIED section?			X
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?			X
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			X
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)			X
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?		X	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		X	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.			X
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?			X
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.	X		

FOR THE RECORD:

1. MODEL LABELING

This review was based on the labeling for Zaditor by Novartis (NDA 21-066/S004: Approved July 20, 2001).

2. LABELING ISSUES:

CONTAINER – 5 mL - Not Satisfactory

Your container label is difficult to read. Increase the information presented on your label clearly and prominently. Refer to 21 CFR 201.10 (i) for the requirements for a drug packaged in a small container. In addition, you may omit the following information:

"Inactive ingredients"

"Storage temperature"

"The address of the manufacturer for and by"

CARTON - 5 mL – Satisfactory in Final Printed Labeling as of July 1, 2004 submission. [Vol. 1.1; Code # cccccc-1203]

INSERT – Satisfactory in Final Printed Labeling as of July 1, 2004 submission. [Vol. 1.1; Revised 12/03]

3. **INACTIVE INGREDIENTS**

There does not appear to be a discrepancy in inactives between the DESCRIPTION and the composition statement.

Ingredients	function
Ketotifen Fumerate, Ph. Eur.	Active
Benzalkonium chloride, USP	(b) (4)
Glycerin (glycerol), USP	
Sodium hydroxide or HCl, NF	
Purified water, USP	

4. **PATENTS/EXCLUSIVITIES**

Patent Data – NDA 21-066

Patent No.	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
6774137	JAN 13,2019	U-599	METHOD FOR TREATING ALLERGIC CONJUNCTIVITIS		
6776982	JAN 13,2019				
6777429	JAN 13,2019				

Firm was asked to update their patent certification. Also, Firm cannot carve out U-599, since this is the only indication for this drug product

Exclusivity-Data – NDA 21-066

Code	Reference	Expiration	Labeling Impact
NCE		July 02, 2004	EXPIRED - NONE

5. **STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON**

- USP: NONE
- RLD: Stored at 4 - 25°C (39 - 77°F)
- ANDA: Store at 4 - 25°C (39 - 77°F)

6. **DISPENSING STATEMENT COMPARISON**

- USP: None.
- RLD: None.
- ANDA: None.

7. **PACKAGE CONFIGURATION**

- RLD: Supplied as 5 mL solution in white 7.5 mL LDPE plastic bottles with controlled plastic dropper tip and white plastic caps.
- ANDA: Supplied as 5 mL solution in white 7.5 mL LDPE plastic bottles with controlled plastic dropper tip and white plastic caps.

8. **CONTAINER/CLOSURE**

The drug product will be packaged in opaque (white) or natural LDPE bottles with natural LDPE dispensing plugs and white (b) (4) closure.

Packaging component	Description
Bottle	(b) (4)
Plug	
closure	

9. **FINISHED DOSAGE FORM**

- RLD: Supplied as a 5 ml Solution
- ANDA: A clear, colorless solution supplied as a 5 mL solution

10. **CAP COLOR**

- RLD: White color cap
- ANDA White color cap - Please note that there is no AAO recommended color coding of

caps for the class of histamine antagonist. Therefore the default color "white" is used.

11. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM

Alcon Manufacturing Ltd.
ASPEX Manufacturing facilities
6201 South Freeway
Fort Worth, TX 76134-2099

Date of Review: **Date of Submission: July 1, 2004**

Primary Reviewer: Beverly Weitzman B. Weitzman **Date:** 2/23/2005

Team Leader: **Date:** 2/24/05

cc:

ANDA: 77-200
DUP/DIVISION FILE
HFD-613/Jgrace (no cc)
V:\FirmsAM\Alcon&REV\77200NA1L.doc
Review

APPROVAL SUMMARY

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 77-200

Date of Submission: April 7, 2005

Applicant's Name: Alcon Laboratories, Inc.

Established Name: Ketotifen Fumarate Ophthalmic Solution USP, 0.025%

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):
Do you have Final Printed Labels and Labeling? YES

- Container Labels: (5 mL) - Satisfactory in Final Print as **April 7, 2005** electronic submission.
  \\cdsesubogd1\N77200\N_000\2005-04-07\Final Printed Labeling for Ketotifen.pdf
- Carton Labeling: (5 mL, 10 mL, 15 mL) – Satisfactory in Final print as of **July 1, 2004** paper submission. [Vol. 1.1; Code # cccccc-1203]
- Professional Package Insert Labeling: Satisfactory in Final Print as of **July 1, 2004** paper submission. [Vol. 1.1; Revised 12/03]

BASIS OF APPROVAL:

- Was this approval based upon a petition? No
- What is the RLD on the 356(h) form: Zaditor Ophthalmic Solution,
- NDA Number: 21-066
- NDA Drug Name: Ketotifen Fumarate Ophthalmic Solution USP, 0.025%
- NDA Firm: Novartis
- Date of Approval of NDA Insert: NDA 21-066/S004: Approved July 20, 2001.
- Has this been verified by the MIS system for the NDA? Yes
- Was this approval based upon an OGD labeling guidance? No
- Basis of Approval for the Container Labels: Side-by-side comparison
- Basis of Approval for the Carton Labels: Side-by-side comparison
- Revisions needed post-approval: **NO**
- Patents/Exclusivities: Refer to chart below.

Patent Data – NDA 21-066

Patent No.	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
6774137	JAN 13,2019	U-599	METHOD FOR TREATING ALLERGIC CONJUNCTIVITIS	III	
6776982	JAN 13,2019			III	
6777429	JAN 13,2019			III	

Exclusivity-Data – NDA 21-066

Code	Reference	Expiration	Labeling Impact
NCE		July 02, 2004	EXPIRED - NONE

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23		X	
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?			X
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?		X	
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?			X
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Labeling(continued)	Yes	No	N.A.
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)			X
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?			X
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
			X

Is the scoring configuration different than the RLD?			
Has the firm failed to describe the scoring in the HOW SUPPLIED section?			X
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?			X
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			X
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)			X
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?		X	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		X	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.			X
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?			X
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.	X		

FOR THE RECORD:

1. **MODEL LABELING**

This review was based on the labeling for Zaditor by Novartis (NDA 21-066/S004: Approved July 20, 2001).

2. **INACTIVE INGREDIENTS**

There does not appear to be a discrepancy in inactives between the DESCRIPTION and the composition statement.

Ingredients	function
Ketotifen Fumerate, Ph. Eur.	(b) (4)
Benzalkonium chloride, USP	
Glycerin (glycerol), USP	
Sodium hydroxide or HCl, NF	
Purified water, USP	

3. **PATENTS/EXCLUSIVITIES**

Patent Data – NDA 21-066

Patent No.	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
6774137	JAN 13,2019	U-599	METHOD FOR TREATING ALLERGIC	III	

			CONJUNCTIVITIS		
6776982	JAN 13,2019			III	
6777429	JAN 13,2019			III	

Exclusivity-Data – NDA 21-066

Code	Reference	Expiration	Labeling Impact
NCE		July 02, 2004	EXPIRED - NONE

5. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

- USP: NONE
- RLD: Stored at 4 - 25°C (39 - 77°F)
- ANDA: Store at 4 - 25°C (39 - 77°F)

6. DISPENSING STATEMENT COMPARISON

- USP: None.
- RLD: None.
- ANDA: None.

7. PACKAGE CONFIGURATION

- RLD: Supplied as 5 mL solution in white 7.5 mL LDPE plastic bottles with controlled plastic dropper tip and white plastic caps.
- ANDA: Supplied as 5 mL solution in white 7.5 mL LDPE plastic bottles with controlled plastic dropper tip and white plastic caps.

8. CONTAINER/CLOSURE - The drug product will be packaged in opaque (white) or natural LDPE bottles with natural LDPE dispensing plugs and white (b) (4) closure.

Packaging component	Description
Bottle	(b) (4)
Plug	
closure	

9. FINISHED DOSAGE FORM

- RLD: Supplied as a 5 ml Solution
- ANDA: A clear, colorless solution supplied as a 5 mL solution

10. CAP COLOR

- RLD: White color cap
- ANDA White color cap - Please note that there is no AAO recommended color coding of caps for the class of histamine antagonist. Therefore the default color white is used.

11. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM

Alcon Manufacturing Ltd.
ASPEX Manufacturing facilities
6201 South Freeway
Fort Worth, TX 76134-2099

Date of Review: **Date of Submission: April 7, 2005**

Primary Reviewer: Beverly Weitzman **Date:** 5/5/2005

B. Weitzman

Team Leader: **Date:** 5/6/2005

---

cc:

ANDA: 77-200
DUP/DIVISION FILE
HFD-613/Jgrace (no cc) .
V:\FIRMSAM\ALCON\LTRS&REV\77-200AP.L.doc
Review

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 77-200

CHEMISTRY REVIEWS

ANDA 77-200

Ketotifen Fumarate Ophthalmic Solution, 0.025%

Alcon, Inc.

Liang-Lii Huang, Ph.D.

OGD/DC1

Table of Contents

Chemistry Review Data Sheet

1. ANDA 77-200 (First generic)

2. REVIEW #: 4

3. REVIEW DATE:
   6/17/08; 7/17/08;8/20/08

4. REVIEWER:
   Liang-Lii Huang, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
None	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	July 1, 2004
Acceptable for filing	July 2, 2004
Telephone Amendment	August 25, 2004
Minor Amendment	February 15, 2005
Minor Amendment	October 26, 2005
Minor Amendment	February 24, 2006
Minor Amendment Request for final approval	April 08, 2008
Telephone amendment	July 8, 2008
Telephone amendment	August 14, 2008

7. NAME & ADDRESS OF APPLICANT:
   Alcon Research, Ltd.
   U.S. Agent for Alcon, Inc.
   Attention: Sarah Contrell
   6201 South Freeway
   Fort Worth, TX 76134-2099
   Tel: 817-551-4517 Fax: 817-551-4630

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A
b) Non-Proprietary Name (USAN):
Ketotifen Fumarate Ophthalmic Solution, 0.025%

9. LEGAL BASIS FOR SUBMISSION:

The basis for this ANDA is Zaditor® (Ketotifen Fumarate) Ophthalmic solution, 0.025%. The NDA 21-066 is held by Novartis.

The applicant filed Paragraph III Patent Certifications in reference to the following patents (04/07/05 updated patent certification):

US Patent No.	Expiration Date
6, 774, 137 (the '137 patent)	January 13, 2019
6, 776, 982 (the '982 patent)	January 13, 2019
6, 777, 429 (the '429 patent)	January 13, 2019

The firm requests approval to market the drug product upon expiration of the '137, '982, and '429 patents and certifies that the '137, '982, and '429 patents expire on January 13, 2019.

There are no unexpired exclusivities for this product in the Orange Book database.

10. PHARMACOL. CATEGORY:

For the temporary prevention of itching of the eye due to allergic conjunctivitis.

11. DOSAGE FORM:

Ophthalmic solution

12. STRENGTH/POTENCY:

0.025%

13. ROUTE OF ADMINISTRATION:

Topical Ophthalmic

14. Rx/OTC DISPENSED: _X_ Rx ___OTC

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

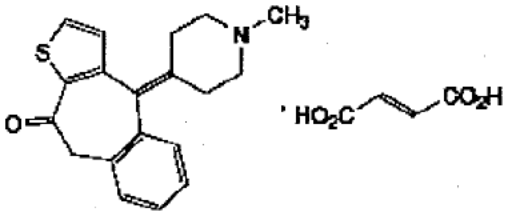
_____SPOTS product – Form Completed

___X___Not a SPOTS product

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

4-(1-Methylpiperidin-4-ylidene)-4,9-dihydro-10*H*-benzo[4,5]cyclohepta[1,2-*b*]thiophen-10-one hydrogen (*E*)-butenedioate.

$C_{23}H_{23}NO_5S$ M.W. 425.5 CAS [34580-14-8]



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
[redacted] (b) (4)				1	Adequate	6/18/08	Reviewed by L L Huang
				4			
				4			
				4			
				3	Adequate	3/17/03	Reviewed by Lu, Y.D.
				4			
				4			

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

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

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
None		

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	Acceptable	5/11/05	D. Obenhuber
EES	Acceptable	8/31/04	
Methods Validation	Requested 1/17/06		
Labeling	Acceptable	5/5/05	B. Weitzman
Bioequivalence	Acceptable	4/21/05	S. Gunther
EA	EA is not required.		
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

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

The Chemistry Review for ANDA 77-200

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This application ANDA 77-200 is approvable.

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

N/A

II. Summary of Chemistry Assessments

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

Drug product

The manufacturing process for the Ketotifen Fumarate Ophthalmic Solution, 0.025% drug product involves (b) (4)

Drug substance

Ketotifen Fumarate is a white to brownish-yellow, fine crystalline powder. It is sparingly soluble in water, slightly soluble in methanol, and very soluble in acetonitrile.

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

The drug product is intended to be used for the temporary prevention of itching of the eye due to allergic conjunctivitis.

Maximum daily dose is 0.05 mg Ketotifen/day. (V 1.7, page 3.2. P.5.6)

For DS, IT = (b) (4) QT (b) (4)%

For DP, IT = (b) (4)%, QT = (b) (4)%

C. Basis for Approvability or Not-Approval Recommendation

This application is approvable.

13 pages are withheld immediately following this page as b4

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Liang Lii Huang
8/28/2008 04:01:20 PM
CHEMIST

James Fan
8/29/2008 08:39:20 AM
CHEMIST

Rosalyn Adigun
8/29/2008 10:41:20 AM
CSO

ANDA 77-200

Ketotifen Fumarate Ophthalmic Solution, 0.025%

Alcon, Inc.

Liang-Lii Huang, Ph.D.

OGD/DC1

Table of Contents

Chemistry Review Data Sheet

1. ANDA 77-200 (First generic)

2. REVIEW #:3

3. REVIEW DATE:
   1/13/05;revised 2/7/06

4. REVIEWER:
   Liang-Lii Huang, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
None	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	July 1, 2004
Acceptable for filing	July 2, 2004
Telephone Amendment	August 25, 2004
Minor Amendment	February 15, 2005
Minor Amendment	October 26, 2005
Minor Amendment	February 24, 2006

7. NAME & ADDRESS OF APPLICANT:
   Alcon Research, Ltd.
   U.S. Agent for Alcon, Inc.
   Attention: Norma Schafer
   6201 South Freeway
   Fort Worth, TX 76134-2099

8. DRUG PRODUCT NAME/CODE/TYPE:

   a) Proprietary Name: N/A
   b) Non-Proprietary Name (USAN):
   Ketotifen Fumarate Ophthalmic Solution, 0.025%

9. LEGAL BASIS FOR SUBMISSION:

The basis for this ANDA is Zaditor® (Ketotifen Fumarate) Ophthalmic solution, 0.025%. The NDA 21-066 is held by Novartis. The applicant filed Paragraph III Patent Certifications in reference to the following patents (04/07/05 updated patent certification):

US Patent No.	Expiration Date
6, 774, 137 (the '137 patent)	January 13, 2019
6, 776, 982 (the '982 patent)	January 13, 2019
6, 777, 429 (the '429 patent)	January 13, 2019

The firm requests approval to market the drug product upon expiration of the '137, '982, and '429 patents and certifies that the '137, '982, and '429 patents expire on January 13, 2019.

There are no unexpired exclusivities for this product in the Orange Book database.

10. PHARMACOL. CATEGORY:

For the temporary prevention of itching of the eye due to allergic conjunctivitis.

11. DOSAGE FORM:

Ophthalmic solution

12. STRENGTH/POTENCY:

0.025%

13. ROUTE OF ADMINISTRATION:

Topical Ophthalmic

14. Rx/OTC DISPENSED: _X_ Rx ___ OTC

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

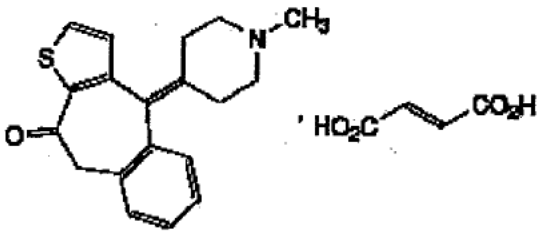
_____SPOTS product – Form Completed

___X___Not a SPOTS product

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

4-(1-Methylpiperidin-4-ylidene)-4,9-dihydro-10*H*-benzo[4,5]cyclohepta[1,2-*b*]thiophen-10-one hydrogen (*E*)-butenedioate.

$C_{23}H_{23}NO_5S$ M.W. 425.5 CAS [34580-14-8]



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)				3	Adequate	7/19/05	Reviewed by L L Huang
				4			
				4			
				4			
				3	Adequate	3/17/03	Reviewed by Lu, Y.D.
				4			
				4			

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review

4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

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

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
None		

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	Acceptable	5/11/05	D. Obenhuber
EES	Acceptable	8/31/04	
Methods Validation	Requested 1/17/06		
Labeling	Acceptable	5/5/05	B. Weitzman
Bioequivalence	Acceptable	4/21/05	S. Gunther
EA	EA is not required.		
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

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

The Chemistry Review for ANDA 77-200

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This application ANDA 77-200 is approvable.

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

N/A

II. Summary of Chemistry Assessments

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

Drug product

The manufacturing process for the Ketotifen Fumarate Ophthalmic Solution, 0.025% drug product involves (b) (4)

Drug substance

Ketotifen Fumarate is a white to brownish-yellow, fine crystalline powder. It is sparingly soluble in water, slightly soluble in methanol, and very soluble in acetonitrile.

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

The drug product is intended to be used for the temporary prevention of itching of the eye due to allergic conjunctivitis.

Maximum daily dose is 0.05 mg Ketotifen/day. (V 1.7, page 3.2. P.5.6)

For DS, IT = (b) (4)%, QT (b) (4)5%

For DP, IT = (b) (4), QT = (b) (4)%

C. Basis for Approvability or Not-Approval Recommendation

This application is approvable.

III. Administrative

A. Reviewer's Signature

Liang-Lii Huang, Ph.D.

B. Endorsement Block

Liang-Lii Huang, Ph.D./1/13/06;2/7/06 L Huang 2/28/06

James Fan, Team Leader/1/17/06;2/7/06

C. CC Block

ANDA 77-200
ANDA DUP 77-200
DIV FILE
Field Copy

10 pages are withheld immediately following this page as b4

cc: ANDA 77-200
ANDA DUP 77-200
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-627 /Liang-Lii Huang, Ph.D. /1/13/06;1/17/06;2/27/06 L Huang 2/28/06

HFD-627/James Fan, Team Leader/ 1/13/06;1/17/06;2/28/06 2/28/06

HFD-617/Rosalyn Adigun, Project Manager/2/28/06

F/T:

V:\FIRMSAM\ALCON\LTRS&REV\77200 rev3.doc

February 28, 2006

TYPE OF LETTER: APPROVABLE

ANDA 77-200

Ketotifen Fumarate Ophthalmic Solution, 0.025%

Alcon, Inc.

Liang-Lii Huang, Ph.D.

OGD/DC1

Table of Contents

Chemistry Review Data Sheet

1. ANDA 77-200 (First generic)

2. REVIEW #:2

3. REVIEW DATE:
   6/23/05;7/5//05

4. REVIEWER:
   Liang-Lii Huang, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
None	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	July 1, 2004
Acceptable for filing	July 2, 2004
Telephone amendment	August 25, 2004
Minor amendment	February 15, 2005

7. NAME & ADDRESS OF APPLICANT:
   Alcon Research, Ltd.
   U.S. Agent for Alcon, Inc.
   Attention: Norma Schafer
   6201 South Freeway
   Fort Worth, TX 76134-2099

8. DRUG PRODUCT NAME/CODE/TYPE:

   a) Proprietary Name: N/A
   b) Non-Proprietary Name (USAN):
   Ketotifen Fumarate Ophthalmic Solution, 0.025%

9. LEGAL BASIS FOR SUBMISSION:

RLD: Zaditor™ (Ketotifen Fumarate) Ophthalmic Solution, 0.025%
NDA 21-066, held by Novartis

Paragraph 1 certification
There are no unexpired patents for this product in the Orange Book database.
Marketing exclusivity for Zaditor™ expires July 2, 2004.

10. PHARMACOL. CATEGORY:
for the temporary prevention of itching of the eye due to allergic conjunctivitis.

11. DOSAGE FORM:
ophthalmic solution

12. STRENGTH/POTENCY:
0.025%

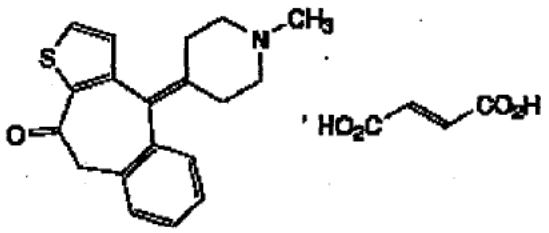
13. ROUTE OF ADMINISTRATION:
topical

14. Rx/OTC DISPENSED: _X_ Rx ___ OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

___X___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:
4-(1-Methylpiperidin-4-ylidene)-4,9-dihydro-10*H*-benzo[4,5]cyclohepta[1,2-*b*]thiophen-10-one hydrogen (*E*)-butenedioate.
$C_{23}H_{23}NO_5S$ M.W. 425.5 CAS [34580-14-8]



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
[redacted] (b) (4)				3	adequate	6/30/05	Reviewed by L L Huang
				4			
				4			
				4			
				3	Adequate	3/17/03	Reviewed by Lu, Y.D.
				4			
				4			

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

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

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
None		

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	Acceptable	5/11/05	D. Obenhuber
EES	acceptable	8/31/04	
Methods Validation	pending		
Labeling	Acceptable	5/5/05	B. Weitzman
Bioequivalence	Acceptable	4/21/05	S. Gunther
EA	EA is not required.		
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

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

The Chemistry Review for ANDA 77-200

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This application ANDA 77-200 is not approvable.

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

N/A

II. Summary of Chemistry Assessments

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

Drug product

The manufacturing process for the Ketotifen Fumarate Ophthalmic Solution, 0.025% drug product involves (b) (4)

Drug substance

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

The drug product is intended to be used for the temporary prevention of itching of the eye due to allergic conjunctivitis.

Maximum daily dose is 0.05 mg ketotifen/day. (V 1.7, page 3.2..P.5.6)

For DS, IT (b) (4)%, QT = (b) (4)%

For DP, IT (b) (4)%, QT (b) (4)%

C. Basis for Approvability or Not-Approval Recommendation

This application is not approvable due to the deficiencies found in the following areas.

(1) The weight loss for the drug product stability studies
(2) HPLC determination of impurities for the drug substance.
(3) The following items should be included in the stability data report.
They are: product name and strength, source of API, the date of manufacture of the drug product, date for packaging, and expiration date.

III. Administrative

A. Reviewer's Signature

Liang-Lii Huang, Ph.D.

B. Endorsement Block

Liang-Lii Huang, Ph.D./6/23/05/7/12/05 L Huang 7/26/25

James Fan, Team Leader/6/23/05 JF for, GK 7/27/05

C. CC Block

ANDA 77-200
ANDA DUP 77-200
DIV FILE
Field Copy

14 pages are withheld immediately following this page as b4

cc: ANDA 77-200
ANDA DUP 77-200
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-627 /Liang-Lii Huang, Ph.D. /6/23/05;6/30/05;7/12/05 L. Huang 7/26/05

HFD-627/ James Fan, Team Leader/ 6/23/05; 6/30/05;7/12/05;7/17/05 For, GK 7/27/05

HFD-617/Ann Vu, Project Manager/7/12/05 7/29/05

F/T: EW 7/22/05

V:\FIRMSAM\ALCON\LTRS&REV\77200 rev2.doc

July 12, 2005

TYPE OF LETTER: NOT APPROVABLE -MINOR/

ANDA 77-200

Ketotifen Fumarate Ophthalmic Solution, 0.025%

Alcon, Inc.

Liang-Lii Huang, Ph.D.

OGD/DC1

Table of Contents

Chemistry Review Data Sheet

1. ANDA 77-200 (First generic)

2. REVIEW #:1

3. REVIEW DATE:
   9/29/04

4. REVIEWER:
   Liang-Lii Huang, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
None	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	July 1, 2004
Acceptable for filing	July 2, 2004
Telephone amendment	August 25, 2004

7. NAME & ADDRESS OF APPLICANT:
   Alcon Research, Ltd.
   U.S. Agent for Alcon, Inc.
   Attention: Norma Schafer
   6201 South Freeway
   Fort Worth, TX 76134-2099

8. DRUG PRODUCT NAME/CODE/TYPE:

   a) Proprietary Name: N/A
   b) Non-Proprietary Name (USAN):
   Ketotifen Fumarate Ophthalmic Solution, 0.025%

9. LEGAL BASIS FOR SUBMISSION:
   RLD: Zaditor™ (Ketotifen Fumarate) Ophthalmic Solution, 0.025%

NDA 21-066, held by Novartis

Paragraph 1 certification
There are no unexpired patents for this product in the Orange Book database.
Marketing exclusivity for Zaditor™ expires July 2, 2004.

10. PHARMACOL. CATEGORY:
for the temporary prevention of itching of the eye due to allergic conjunctivitis.

11. DOSAGE FORM:
ophthalmic solution

12. STRENGTH/POTENCY:
0.025%

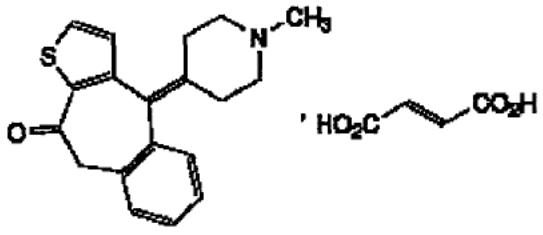
13. ROUTE OF ADMINISTRATION:
topical

14. Rx/OTC DISPENSED: _X_ Rx ___ OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

___X___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:
4-(1-Methylpiperidin-4-ylidene)-4,9-dihydro-10*H*-benzo[4,5]cyclohepta[1,2-*b*]thiophen-10-one hydrogen (*E*)-butenedioate.
$C_{23}H_{23}NO_5S$ M.W. 425.5 CAS [34580-14-8]



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
[redacted] (b) (4)				1	inadequate	9/23/04	Reviewed by L L Huang
				4			
				4			
				4			
				3	Adequate	3/17/03	Reviewed by Lu, Y.D.
				4			
				4			

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

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

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
None		

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	Pending		
EES	acceptable	8/31/04	
Methods Validation	pending		
Labeling	pending		
Bioequivalence	pending		
EA	EA is not required.		
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

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

The Chemistry Review for ANDA 77-200

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This application ANDA 77-200 is not approvable.

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

N/A

II. Summary of Chemistry Assessments

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

Drug product

The manufacturing process for the Ketotifen Fumarate Ophthalmic Solution, 0.025% drug product involves (b) (4)

Drug substance

Ketotifen Fumarate is a white to brownish-yellow, fine crystalline powder. It is sparingly soluble in water, slightly soluble in methanol, and very soluble in acetonitrile.

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

The drug product is intended to be used for the temporary prevention of itching of the eye due to allergic conjunctivitis.

Maximum daily dose is 0.05 mg ketotifen/day. (V 1.7, page 3.2. P.5.6)

C. Basis for Approvability or Not-Approval Recommendation

This application is not approvable due to the deficiencies found in the following areas.

(1) DMF (b) (4) is inadequate.

(2) The impurity specifications for the drug substance and drug product.

(3) HPLC determination of impurities for the drug substance and drug product.

III. Administrative

A. Reviewer's Signature

Liang-Lii Huang, Ph.D.

B. Endorsement Block

Liang-Lii Huang, Ph.D./9/29/04;10/29/04 L Huang 11/4/04 ; 11/9/04

James Fan, Team Leader/9/29/04;10/29/04 11/6/04 11/10/04

C. CC Block

ANDA 77-200
ANDA DUP 77-200
DIV FILE
Field Copy

13 pages are withheld immediately following this page as b4

cc: ANDA 77-200
ANDA DUP 77-200
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-627 /Liang-Lii Huang, Ph.D. /10/5/04;10/29/04 L Huang 11/4/04; 11/9/04

HFD-627/ James Fan, Team Leader/ 10/5/04;10/29/04 11/6/04

HFD-617/Ann Vu, Project Manager/10/29/04 11/10/04

F/T:ard/11/3/04

V:\FIRMSAM\ALCON\LTRS&REV\77200 rev1.doc

October 29, 2004

TYPE OF LETTER: NOT APPROVABLE -MINOR/

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 77-200

BIOEQUIVALENCE REVIEWS

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	77-200
Drug Product Name	Ketotifen Fumarate Ophthalmic Solution
Strength	0.025%
Applicant Name	Alcon, Inc.
Address	P.O. Box 62, Bosch 69, CH-6331, Hunenberg, Switzerland
U.S. Agent	Alcon Research Ltd. R7-18, 6201 South Freeway, Fort Worth, TX 76134-2099
Submission Date(s)	July 1, 2004
Amendment Date(s)	N/A
Reviewer	Sheryl D. Gunther
First Generic	Yes
File Location	v:\firmsam\alcon\ltrs&rev\77200W0704.doc

I. Executive Summary

The firm requested a waiver of in-vivo bioequivalence testing requirements for its test product, Ketotifen Fumarate Ophthalmic Solution, 0.025%. The reference-listed drug (RLD) is Novartis Ophthalmics' Zaditor® (ketotifen fumarate) Ophthalmic Solution, 0.025%. In support of the biowaiver request, the firm has submitted comparative formulations of its Ketotifen Fumarate Ophthalmic Solution, 0.025%, and Zaditor® (ketotifen fumarate) Ophthalmic Solution, 0.025%. The biowaiver request is granted based on 21 CFR §320.22(b)(1). The application is acceptable with no deficiencies.

II. Table of Contents

III. Submission Summary

A. Drug Product Information

Test Product	Ketotifen Fumarate Ophthalmic Solution, 0.025%
Reference Product	Zaditor® (ketotifen fumarate) Ophthalmic Solution, 0.025%
RLD Manufacturer	Novartis Ophthalmics
NDA No.	21-066
RLD Approval Date	July 2, 1999
Indication	indicated for the temporary prevention of itching of the eye due to allergic conjunctivitis

B. Background

This submission is the designated first generic for this drug product. ANDA 77-354 (Apotex, Inc; submission date 12/20/2004) for Ketotifen Fumarate Ophthalmic Solution, 0.025%, is pending bioequivalence review.

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. Ketotifen has been shown to have little systemic exposure following topical ocular administration.

The RLD is supplied as a 5 mL sterile ophthalmic solution for topical administration to the eyes in a white 7.5 mL plastic bottle with dropper tip and closure. The test product is also a sterile ophthalmic solution with the same route of administration and therapeutic indication. It is also supplied as a 5 mL solution in a white 7.5 mL plastic bottle with dropper tip and closure. (Reviewer's Note: The RLD is also available in a 1 mL volume.)

C. Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fasting	No	--
Single-dose fed	No	--
Steady-state	No	--
In vitro dissolution	No	--
Waiver requests	Yes	1
BCS Waivers	No	--
Vasoconstrictor Studies	No	--
Clinical Endpoints	No	--
Failed Studies	No	--
Amendments	No	--

D. Formulation

Location in appendix	Section IV, Page 5
Inactive ingredients within IIG Limits (yes or no)	Yes
If no, list ingredients outside of limits	--
If a tablet, is the product scored? (yes or no)	--
If yes, which strengths are scored?	--
Is scoring of RLD the same as test? (yes or no)	--
Formulation is acceptable (yes or no)	Yes
If not acceptable, why?	--

E. Waiver Request(s)

Strengths for which waivers requested	0.025%
Regulation cited	21 CFR §320.22(b)(1)
Proportional to strength tested in vivo (yes or no)	N/A
Dissolution is acceptable (yes or no)	N/A
Waiver granted (yes or no)	Yes

F. Deficiency Comments

None

G. Recommendations

The Division of Bioequivalence agrees that the information submitted by Alcon, Inc. demonstrates that its Ketotifen Fumarate Ophthalmic Solution, 0.025%, supplied as a sterile ophthalmic solution, falls under the criteria set forth in 21 CFR §320.22(b)(1) of the Bioavailability/Bioequivalence Regulations.

Therefore, a waiver of *in vivo* bioequivalence study requirements is granted for Ketotifen Fumarate Ophthalmic Solution, 0.025%. The test product, Ketotifen Fumarate Ophthalmic Solution, 0.025%, is deemed bioequivalent to Novartis Ophthalmics' Zaditor® (ketotifen fumarate) Ophthalmic Solution, 0.025%.

Sheryl Gunther — 4/21/2005
Sheryl Gunther, Reviewer, Branch V — Date

Moheb H. Makary — 4/21/2005
Moheb H. Makary, Ph.D., Acting Team Leader, Branch V — Date

for Barbara M Davit — 4/21/05
Dale P. Conner, Pharm.D. — Date
Director, Division of Bioequivalence
Office of Generic Drugs

IV. Appendix

H. Formulation Data

Ingredients	Test Product Alcon Inc.'s Ketotifen Fumarate Ophthalmic Solution 0.025% (ANDA# 77-200)		RLD Novartis Ophthalmic's Zaditor® (ketotifen fumarate) Ophthalmic Solution 0.025% (NDA# 21-066)	
	mg/mL	% w/v	mg/mL	% w/v
Ketotifen Fumarate	0.345(1)	0.0345(1)	0.345(1)	0.0345(1)
Benzalkonium chloride, NF				
Glycerin (glycerol), USP				
Sodium hydroxide, NF and/or Hydrochloric acid, NF				
Purified Water, USP				

(b) (4)

The formulation for the RLD has been verified in COMIS, the on-line product labeling for Zaditor® provided by Novartis Ophthalmics, and the Microbiology Review of NDA 21-066, review date 2/9/1999.

Reviewer's Comments:

(1) Ketotifen Fumarate 0.345 mg/mL (0.0345 % w/v) is equivalent to Ketotifen 0.25 mg/mL (0.025% w/v) base.

(2) The test product is adjusted to a pH of (b) (4). The RLD product labeling indicates the RLD has a pH of 4.4 to 5.8.

(3) The quantity of the inactive ingredient, glycerin (glycerol), in the test and reference formulations differs by approximately (b) (4) % w/v. Thus, the concentration of glycerin in the test product differs by less than 5% of the concentration in the RLD.

(4) The test and reference products are qualitatively (Q1) the same and quantitatively (Q2) essentially the same.[1]

[1] Quantitatively *essentially the same* has been determined by CDER to mean that the concentration or amount of the inactive ingredient(s) in the test product would not differ by more than 5 percent of the concentration or amount in the reference listed drug. (CDER Draft Guidance for Industry: *Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action,* posted April 2003.)

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 77-200 APPLICANT: Alcon, Inc.

DRUG PRODUCT: Ketotifen Fumarate Ophthalmic Solution, 0.025%

The Division of Bioequivalence has completed its review and has no further questions at this time.

Please note that the bioequivalence comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalence information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

for Barbara M. Davit

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

CC: ANDA 77-200
ANDA DUPLICATE
DIVISION FILE
HFD-650/ Bio Drug File
HFD-650/ Reviewer S. Gunther
HFD-650/ Project manager B. Fritsch
HFD-650/ Team Leader M. Makary

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Endorsements: (Final with Dates)
HFD-650/S. Gunther 4/21/2005
HFD-650/M. Makary 4/21/2005
HFD-650/D.P. Conner 4/21/05

BIOEQUIVALENCE – ACCEPTABLE Submission Date: July 1, 2004

1. WAIVER (WAI) Strengths: 0.025%
Outcome: AC

Outcome Decisions: AC - Acceptable
WinBio Comments: AC

APR 21 2005

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA #: 77-200 **SPONSOR:** Alcon, Inc.
DRUG & DOSAGE FORM: Ketotifen Fumarate Ophthalmic Solution
STRENGTH(S): 0.025%
TYPES OF STUDIES: N/A
CLINICAL STUDY SITE(S): N/A
ANALYTICAL SITE(S): N/A

STUDY SUMMARY: N/A
DISSOLUTION: N/A.

DSI INSPECTION STATUS

Inspection needed:	No	**Inspection status:**	**Inspection results:**
First Generic	Yes		
New facility			
For cause			
Other			

Proposed Dissolution Method and Specifications from Original Submission Acceptable?
Yes N/A No _____ (If no, project Manager should verify and sign below when acknowledgement amendment is received)

DBE Dissolution Method and Specifications acknowledged by firm? Yes N/A No ___

AMENDMENT DATE: _____

PROJECT MANAGER: _____ **DATE:** _____

PRIMARY REVIEWER: Sheryl Gunther, Pharm.D. **BRANCH:** V
INITIAL: SLG DATE: 4/21/2005

ACTING TEAM LEADER: Moheb H. Makary, Ph.D. **BRANCH:** V
INITIAL: moheb h. makary DATE: 4/21/2005

for **DIRECTOR, DIVISION OF BIOEQUIVALENCE:** Dale P. Conner, Pharm.D.
INITIAL: Barbara M Davit DATE: 4/21/05

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 77-200

MICROBIOLOGY REVIEWS

Drfile

Product Quality Microbiology Review
Review for HFD-620

March 11, 2005

ANDA: 77-200

Drug Product Name
Proprietary: n/a
Non-proprietary: Ketotifen Fumarate Ophthalmic Solution 0.025%
Drug Product Classification: n/a

Review Number: #1

Subject of this Review
Submission Date: July 1, 2004
Receipt Date: July 2, 2004
Consult Date: n/a
Date Assigned for Review: March 11, 2005

Submission History (for amendments only)
Date(s) of Previous Submission(s): none
Date(s) of Previous Micro Review(s): none

Applicant/Sponsor

Name:	Alcon, Inc.
Address:	P.O. Box 62 Bosch 69 CH-6331 Hunenberg Switzerland
Representative:	Alcon Research, Ltd. 6201 South Freeway Fort Worth, TX 76134
Contact Person:	Norma Schafer
Telephone:	817-551-8568

Name of Reviewer: Donald C. Obenhuber

Conclusion: Recommended

Product Quality Microbiology Data Sheet

A. 1. **TYPE OF SUPPLEMENT:** n/a

2. **SUPPLEMENT PROVIDES FOR:** n/a

3. **MANUFACTURING SITE:** Alcon's ASPEX facility in Fort Worth, TX

4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:** preserved, multi-dose formulation of 0.025% sterile ophthalmic solution packaged as a 5 ml fill in (b) (4) LDPE (b) (4) container/closure systems

5. **METHOD(S) OF STERILIZATION:** Aseptic Fill

6. **PHARMACOLOGICAL CATEGORY:** Indicated for the temporary relief of ocular itching due to seasonal allergic conjunctivitis.

B. **SUPPORTING/RELATED DOCUMENTS:**

C. **REMARKS:** The manufacturing process and validation has been previously submitted and "recommended" for the 5 mL and 10 mL (b) (4) systems at the ASPEX facility (ANDA (b) (4)).

Executive Summary

I. Recommendations

A. Recommendation on Approvability – Recommended

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable – n/a

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology – The bulk drug solution is sterile [redacted] (b) (4)

B. Brief Description of Microbiology Deficiencies – none identified

C. Assessment of Risk Due to Microbiology Deficiencies – n/a

III. Administrative

A. Reviewer's Signature Donald C Obenhuber 5/9/05

B. Endorsement Block Lynn A. Enos (for N. Sweeney) 5/11/05
Donald C. Obenhuber, Ph.D.
N. Sweeney, Ph.D.

C. CC Block
cc:
Original ANDA 77-200
Division File
Field Copy

filename: v:\microrev\77-200.doc

17 pages are withheld immediately following this page as b4

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 77-200

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

OGD APPROVAL ROUTING SUMMARY

ANDA # 77-200 Applicant Alcon Inc.
Drug Ketotifen Fumarate Ophthalmic Solution, Strength(s) 0.025%

APPROVAL ☒ **TENTATIVE APPROVAL** ☐ **SUPPLEMENTAL APPROVAL (NEW STRENGTH)** ☐ **OTHER** ☐

REVIEWER: **DRAFT Package** **FINAL Package**

1. **Martin Shimer** Date 1 July 2008 Date 9/2/08
Chief, Reg. Support Branch Initials MHS Initials rlw

Contains GDEA certification: Yes ☒ No ☐ Determ. of Involvement? Yes ☐ No ☒
(required if sub after 6/1/92)
Pediatric Exclusivity System
RLD = Zaditor NDA#21-066
Patent/Exclusivity Certification: Yes ☒ No ☐ Date Checked N/A
If Para. IV Certification- did applicant Nothing Submitted ☐
Notify patent holder/NDA holder Yes ☐ No ☐ Written request issued ☐
Was applicant sued w/in 45 days: Yes ☐ No ☐ Study Submitted ☐
Has case been settled: Yes ☐ No ☐ Date settled:
Is applicant eligible for 180 day
Generic Drugs Exclusivity for each strength: Yes ☐ No ☒
Date of latest Labeling Review/Approval Summary _____
Any filing status changes requiring addition Labeling Review Yes ☐ No ☒
Type of Letter: Full Approval.
Comments: ANDA originally submitted on 7/2/2004, BOS=Zaditor, NDA 21-066, PI cert provided. ANDA ack for filing on 7/2/2004 (LO dated 8/26/2004). On 10/19/2006, NDA 21-066 was converted from Rx to OTC status. Firm submitted information to convert the marketing status of their unapproved ANDA from Rx to OTC.

There are no remaining patents or exclusivities which protect the RLD Zaditor OTC. This ANDA is eligible for Full Approval.

2. Project Manager, Rosalyn Adigun Team 3 Review Support Branch Date June 26, 2008 Date _____
Initials RA Initials _____

Original Rec'd date July 1, 2004
Date Acceptable for Filing July 2, 2004
Patent Certification (type) III
Date Patent/Exclus.expires N/A
Citizens' Petition/Legal Case Yes ☐ No ☒
(If YES, attach email from PM to CP coord)
First Generic Yes ☐ No ☒
Priority Approval Yes ☐ No ☒
(If yes, prepare Draft Press Release, Email it to Cecelia Parise)

EER Status Pending ☒ Acceptable ☐ OAI ☐
Date of EER Status _____
Date of Office Bio Review April 21, 2005
Date of Labeling Approv. Sum June 24, 2008
Date of Sterility Assur. App. May 11, 2005
Methods Val. Samples Pending Yes ☐ No ☒
MV Commitment Rcd. from Firm Yes ☐ No ☒
Modified-release dosage form: Yes ☐ No ☒
Interim Dissol. Specs in AP Ltr: Yes ☒

Acceptable Bio reviews tabbed Yes ☒ No ☐
Bio Review Filed in DFS: Yes ☐ No ☒
Suitability Petition/Pediatric Waiver
Pediatric Waiver Request Accepted ☐ Rejected ☐ Pending ☐
Previously reviewed and tentatively approved ☒ Date March 17, 2006
Previously reviewed and CGMP def. /NA Minor issued ☐ Date _____

Comments:TA to full approval (OTC)

3. Labeling Endorsement
Reviewer:
DateJune 24, 2008
Name/Initialsra for pb

Labeling Team Leader:
DateJune 24, 2008
Name/Initialsra for jfg

Comments:

Ap summ in DFS

4. David Read **(PP IVs Only)** Pre-MMA Language included ☐ Date 9/2/08
OGD Regulatory Counsel, Post-MMA Language Included ☐ Initials rlw/for
Comments: There are no patents or exclusivity listed in the current "Orange Book" for this drug product.

5. Div. Dir./Deputy Dir.
Chemistry Div. I

Date8/28/08
InitialsRMP

Comments:Except for EER the CMC section is satisfactory for AP.

See note below regarding EES status/rlw 9/2/08.

6. Frank Holcombe **First Generics Only** Date 9/2/08
Assoc. Dir. For Chemistry Initials rlw/for Comments: (First generic drug review)
N/A. Multiple ANDAs have been approved for this OTC drug product.

7. Vacant Date_____ Deputy Dir., DLPS
Initials_____
RLD = Zaditor Ophthalmic Solution 0.025%(base)
Novartis Pharmaceuticals Corporation NDA 21-066

8. Peter Rickman Date9/2/08
Director, DLPS Initialsrlw/for
Para.IV Patent Cert: Yes☐ No☐;Pending Legal Action: Yes ☐ No ☐; Petition: Yes☐ No☐ Comments: This ANDA was granted tentative approval on March 17, 2006. Final approval was blocked at that time by three lsited patents that were due to expire on Janaury 13, 2019 (Alcon has provided paragraph III certifications to these patents). Subsequently, Novartis's Zaditor Ophthalmic Solution was converted to OTC status and no patents were listed in the "Orange Book" for the drug product subsequent to this change. On March 25, 2008, Alcon amended its ANDA to provide for a paragraph I certification. Final-printed labeling (FPL) to reflect the OTC status of this drug product was submitted on April 7, 2008.

Final-printed labeling (FPL) found acceptable for approval 6/24/08.

CMC found acceptable for approval (Chemistry Review #4) 8/28/08.

OR

8. Robert L. West — Date 9/2/08
Deputy Director, OGD — Initials rlw/for
Para.IV Patent Cert: Yes☐ No☒; Pending Legal Action: Yes☐ No☒; Petition: Yes☐ No☒
Press Release Acceptable ☐
Comments: At the time of tentative approval, all facilities including the API suppler, [redacted] (b)(4) were found acceptable. At present, an update is pending for [redacted] (b)(4) in EES. Refer to my email dated August 29, 2008 that details OGD's position with respect to the approval of this ANDA. It appears that a reinspection of [redacted] (b)(4) has been assigned but remains unscheduled. No "OAI" Alerts are noted for this facility and there are [redacted] (b)(4) ANDAs for this drug product that utilize [redacted] (b)(4) as their API supplier. A copy of this email has been placed in DFS. In the absence of a response from OC, OGD will proceed to approve this ANDA.

There are no patents or exclusivity listed in the current "Orange Book" for this drug product.

This ANDA is recommended for approval (Over-the-Counter).

9. Gary Buehler — Date 9/2/08
Director, OGD — Initials rlw/for
Comments:
First Generic Approval ☐ PD or Clinical for BE ☐ Special Scientific or Reg.Issue ☐

Press Release Acceptable ☐

10. Project Manager, Rosalyn Adigun Team — Date September 2, 2008

Review Support Branch — Initials RA
_____Date PETS checked for first generic drug (just prior to notification to firm)

Applicant notification:
10:23 am Time notified of approval by phone
10:26 am Time-approval letter faxed

FDA Notification:
September 2, 2008 Date e-mail message sent to "CDER-OGDAPPROVALS" distribution list.
September 2, 2008 Date Approval letter copied to \\CDS014\DRUGAPP\ directory.

EER DATA:

EES Data for: 077200

*** Compliance Recommendations ***

App No	Doc Seq No	Date	OC Recommendation
077200	000	8/31/2004	ACCEPTABLE

*** EER Table ***

CFN	Name	Profile Code	Last Milestone Name	Last Milestone Date	Last Status	Last Status Date	OAI Alert/ Effective Date
[redacted]						(b) (4)	None
1610287	ALCON LABORATORIES INC	SNI	OC RECOMMENDATION	4/29/2008	AC	4/29/2008	None
[redacted]						(b) (4)	None
							None

Also refer to the memo/email dated August 29, 2008 from Robert L. West to CDER EESQUESTIONS.

COMIS TABLE:

Comis Application Table Data for Application No: 077200

*** Note: For Enterprise Search Files you may have to click and close the new window on first use*

Back to Search Form | *COMIS Pool Reviewers* | **ES DFS Files Only** | **ES - All Files** | **EDR** | **Additions**

Drug Name: KETOTIFEN FUMARATE

Potency: 0.025 % Dosage Form: SOL APPL Type: N

Applicant: ALCON

Status Code: PN Status Date: 7/9/2008 Clock Date: 7/2/2004 USP: N Org: 600

Therapeutic Drug Class: ANTIHISTAMINE

Patent Certification: 1 Patent Expiration Date: PEPFAR:

Incom Doc Type	*Seq No*	*Supp Mod Type*	*Letter Date*	*Stamp Date*	*Decision Code*	*Decision Date*	*Status code*	*Status Date*	*Priority Flag*	*Document ID Click to see Assignment*	*Priority Date*
N *Volume Locator*	000		7/1/2004	7/2/2004	NM	11/15/2004	PN	7/9/2008	1	2587733	4/8/2008
N *Volume Locator*	000	MC	8/25/2004	8/26/2004	CL	8/26/2004				2609219	
N *Volume Locator*	000	MC	11/16/2004	11/17/2004	CL	11/18/2004				2638249	
N *Volume Locator*	000	AM	2/15/2005	2/16/2005	NM	8/5/2005				2671444	
N *Volume Locator*	000	AF	4/7/2005	4/8/2005	TA	3/17/2006				2691888	
N *Volume Locator*	000	MC	8/5/2005	8/8/2005	CL	8/8/2005				2739441	
N *Volume Locator*	000	AM	10/26/2005	10/27/2005	TA	3/17/2006				2767233	
N *Volume Locator*	000	AM	2/24/2006	2/24/2006	TA	3/17/2006				2914111	

N ➪*Volume Locator*	000	AM	2/28/2006	3/1/2006	OP	3/1/2006				2906291	
N ➪*Volume Locator*	000	AF	3/24/2008	3/25/2008	OP	3/25/2008				3930970	
N ➪*Volume Locator*	000	XP	3/25/2008	3/26/2008	CL	3/26/2008				3931346	
N ➪*Volume Locator*	000	AM	4/7/2008	4/8/2008	OP	4/8/2008				3937354	
N ➪*Volume Locator*	000	AF	6/11/2008	6/12/2008	OP	6/12/2008				3967771	
N ➪*Volume Locator*	000	MC	6/11/2008	6/13/2008	CL	6/13/2008				3968039	
N ➪*Volume Locator*	000	AM	7/8/2008	7/9/2008	OP	7/9/2008				3980372	
N ➪*Volume Locator*	000	AA	7/25/2008	7/28/2008	OP	7/28/2008				3990500	
N ➪*Volume Locator*	000	AA	8/14/2008	8/15/2008	OP	8/15/2008				4000573	***Comis Document Table Data***

ORANGE BOOK PRINT OFF:

Patent and Exclusivity Search Results from query on Appl No 021066 Product 002 in the OB_OTC list.

Patent Data

There are no unexpired patents for this product in the Orange Book Database.

[Note: Title I of the 1984 Amendments does not apply to drug products submitted or approved under the former Section 507 of the Federal Food, Drug and Cosmetic Act (antibiotic products). Drug products of this category will not have patents listed.]

Exclusivity Data

There is no unexpired exclusivity for this product.

View a list of all patent use codes
View a list of all exclusivity codes

Return to Electronic Orange Book Home Page

FDA/Center for Drug Evaluation and Research
Office of Generic Drugs
Division of Labeling and Program Support
Update Frequency:
Orange Book Data - **Monthly**
Generic Drug Product Information & Patent Information - **Daily**
Orange Book Data Updated Through July, 2008
Patent and Generic Drug Product Data Last Updated: August 29, 2008

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Rosalyn Adigun
9/2/2008 01:12:31 PM

From: West, Robert L
Sent: Tuesday, September 02, 2008 9:39 AM
To: Adigun, Rosalyn
Subject: FW: ANDA 77-200 FOR ALCON'S KETOTIFEN FUMARATE OPHTHALMIC SOLUTION -
Rosalyn:

Please file this email in DFS for Alcon's ANDA 77-200.

Thanks,

Bob

From: West, Robert L
Sent: Friday, August 29, 2008 10:59 AM
To: CDER EESQUESTIONS
Cc: Adigun, Rosalyn; Rickman, William P; Rivera Martinez, Edwin
Subject: ANDA 77-200 FOR ALCON'S KETOTIFEN FUMARATE OPHTHALMIC SOLUTION -

Dear EES:

OGD currently has an approval package for Alcon's ANDA 77-200 for Ketotifen Fumarate Ophthalmic Solution, 0.025%. All facilities in EES are currently acceptable for this ANDA with the exception of the ANDA supplier:

(b) (4)

This ANDA was granted tentative approval on March 17, 2006. (b) (4) was acceptable at that time. In anticipation of final approval, an EES update request was submitted in April 2008. Currently, a reinspection of (b) (4) is assigned, but there is no indication that it has been scheduled. There are no "OAI" Alerts noted in the EES system for this facility.

Furthermore, (b) (4) is currently the API supplier for the following (b) (4) ANDAs:

(b) (4)

Based upon the fact that Alcon was granted tentative approval with API obtained from (b) (4) and the fact that there are currently (b) (4) ANDAs in the marketplace for this drug product using API from (b) (4) it would appear to be reasonable for OGD to proceed to approve Alcon's ANDA.

Does OC concur that this is a reasonable approach?

Thank you,

Bob

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Rosalyn Adigun
9/2/2008 10:06:42 AM
CSO

Alcon
RESEARCH, Ltd.

August 14, 2008

Sarah Cantrell, M.A. R7-18
Asst. Director, Regulatory Affairs
6201 South Freeway
Ft. Worth, Texas 76134-2099

Mr. Gary Buehler
Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place
Rockville, MD 20855-2773

Re: **ANDA 77-200**
Ketotifen Fumarate Ophthalmic Solution, 0.025%
TELEPHONE AMENDMENT: (b) (4) Information

Dear Mr. Buehler:

Alcon is providing additional (b) (4) information for ANDA 77-200, Ketotifen Fumarate Ophthalmic Solution as requested by Dr. Jim Fan, Chemistry Team Leader on July 17, 2008. As requested, this information has been sent via facsimile to Dr. Liang Lii Huang.

A true and accurate copy of this amendment has been submitted to the FDA Dallas Distract Office as a Field Copy.

Alcon, Inc. has previously submitted a Letter of Non-Repudiation.

We appreciate the Agency's time and consideration spent in the review of this application. If there are any questions, regarding the content or format of this application, do not hesitate to contact the undersigned directly at (817) 551-4517 or via facsimile to (817) 551-4630

Sincerely,

Sarah Cantrell

Sarah J. Cantrell, MA
Assistant Director, Regulatory Affairs

Enclosure

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: September 30, 2008
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Alcon, Inc.	August 14, 2008
TELEPHONE NO. *(Include Area Code)*	FACSIMILE *(FAX)* Number *(Include Area Code)*
817-551-8568	817-551-4630
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued)*: P.O. Box 62 Bosch 69 CH-6331, Hunenberg Switzerland	AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE Alcon Research, Ltd. R7-18 Phone: 817-551-8568 6201 South Freeway Fax: 817-551-4630 Fort Worth, Texas 76134-0450

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* **77-200**

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Ketotifen Fumerate Ophthalmic Solution	

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*

CODE NAME *(If any)*

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Solution	0.025%	Topical, ocular

(PROPOSED) INDICATION(S) FOR USE:
Temporarily relieves itchy eyes due to pollen, ragweed, grass, animal hair and dander.

APPLICATION DESCRIPTION

APPLICATION TYPE *(check one)* ☐ NEW DRUG APPLICATION (CDA, 21 CFR 314.50) ☒ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94) ☐ BIOLOGICS LICENSE APPLICATION (BLA, 21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☐ 505 (b)(1) ☐ 505 (b)(2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

Name of Drug Zaditor Holder of Approved Application Novartis

TYPE OF SUBMISSION *(check one)* ☐ ORIGINAL APPLICATION ☒ AMENDMENT TO APENDING APPLICATION ☐ RESUBMISSION ☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☒ OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION:

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION
Telephone Amendment (b) (4) Additional Information

PROPOSED MARKETING STATUS *(check one)* ☐ PRESCRIPTION PRODUCT (Rx) ☒ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 THIS APPLICATION IS ☐ PAPER ☒ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

This application contains the following items: *(Check all that apply)*	
☐	1. Index
☐	2. Labeling *(check one)* ☐ Draft Labeling ☒ Final Printed Labeling
☐	3. Summary (21 CFR 314.50 (c))
☒	4. Chemistry section
☒	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
☐	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
☐	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
☐	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
☐	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
☐	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
☐	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
☐	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
☐	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
☐	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
☐	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
☐	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
☐	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
☐	15. Establishment description (21 CFR Part 600, if applicable)
☐	16. Debarment certification (FD&C Act 306 (k)(1))
☐	17. Field copy certification (21 CFR 314.50 (l)(3))
☐	18. User Fee Cover Sheet (Form FDA 3397)
☐	19. Financial Information (21 CFR Part 54)
☐	20. OTHER *(Specify)*

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE:
Sarah Cantrell	Sarah Cantrell, Asst. Director, Regulatory Affairs	8/14/08

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
6201 South Freeway, Fort Worth, Texas 76134-2099	(817) 551-4517

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research (HFM-99)
1401 Rockville Pike
Rockville, MD 20852-1448

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Response to

FDA
(Issues of 17 July 2008)

on

Ketotifen Fumarate Ophthalmic Solution, 0.025%

ISSUE 1:

Provide manufacturer and Alcon certificates of analysis for the excipients benzalkonium chloride and glycerin which include both specifications and reported values. Alternately, if the manufacturer [redacted] (b) (4) then a statement from the supplier stating this information will be acceptable.

RESPONSE:

[redacted] (b) (4)

ISSUE 2:

Provide a revised product specification to include the test for [redacted] (b) (4)

RESPONSE:

The drug product release specifications for Ketotifen Fumerate Ophthalmic Solution, 0.025%, are revised to include a test for [redacted] (b) (4) (see the revised Section 3.2.P.5.1 in the Appendix to this response as Tab 5).

The total daily dose of the drug product is one drop twice daily, which is less than 10 grams/day. All drug substance and excipient components of the drug product have [redacted] (b) (4) acceptance limits that fall within the [redacted] (b) (4) (b) (4)

ISSUE 3:

Clarify who is the proposed manufacturer for glycerin. The original submission included (b) (4) and the July 8, 2008 amendment included a manufacturer questionnaire from (b) (4). COAs containing (b) (4) data are required from all proposed manufacturers.

RESPONSE:

The current supplier of glycerin is (b) (4).

Appendix

Contents

Alcon
RESEARCH, Ltd.

July 25, 2008

Sarah Cantrell, M.A. R7-18
Asst. Director, Regulatory Affairs
6201 South Freeway
Ft. Worth, Texas 76134-2099

Mr. Gary Buehler
Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place
Rockville, MD 20855-2773

Re: **ANDA 77-200**
Ketotifen Fumarate Ophthalmic Solution, 0.025%
INTENT TO AMEND: (b) (4) Issue of July 17, 2008

Dear Mr. Buehler:

Reference is made to the telephone request of July 17, 2008 regarding additional (b) (4) data for Ketotifen Fumarate Ophthalmic Solution, 0.025% Pursuant to the conditions outlined under 21 CFR 314.120, please be advised that Alcon intends to file an amendment to the pending application.

Alcon, Inc. has previously submitted a Letter of Non-Repudiation.

If you require additional information or I can assist you further, please contact me at 817-551-4517.

Sincerely,

Sarah Cantrell

Sarah J. Cantrell, MA
Assistant Director, Regulatory Affairs

Enclosure

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: September 30, 2008
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Alcon, Inc.	July 25, 2008
TELEPHONE NO. *(Include Area Code)*	FACSIMILE *(FAX)* Number *(Include Area Code)*
817-551-8568	817-551-4630
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):*	AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE
P.O. Box 62 Bosch 69 CH-6331, Hunenberg Switzerland	Alcon Research, Ltd. R7-18 Phone: 817-551-8568 6201 South Freeway Fax: 817-551-4630 Fort Worth, Texas 76134-0450

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* **77-200**

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Ketotifen Fumerate Ophthalmic Solution	

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*	CODE NAME *(If any)*

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Solution	0.025%	Topical, ocular

(PROPOSED) INDICATION(S) FOR USE:
Temporarily relieves itchy eyes due to pollen, ragweed, grass, animal hair and dander.

APPLICATION DESCRIPTION

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IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☐505 (b)(1) ☐ 505 (b)(2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug Zaditor Holder of Approved Application Novartis

TYPE OF SUBMISSION *(check one)* ☐ ORIGINAL APPLICATION ☒ AMENDMENT TO APENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT
☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION
Telephone Amendment: (b) (4) Information

PROPOSED MARKETING STATUS *(check one)* ☐ PRESCRIPTION PRODUCT (Rx) ☒ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 THIS APPLICATION IS ☐ PAPER ☒ PAPER AND ELECTRONIC ☐ ELECTRONIC

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Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

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☐	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
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☒	20. OTHER *(Specify)* Intent to Amend

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

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3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
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5. Regulations on making changes in application in FD&C Act section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE:
Sarah Cantrell	Sarah Cantrell, Asst. Director, Regulatory Affairs	7/25/08

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
6201 South Freeway, Fort Worth, Texas 76134-2099	(817) 551-4517

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research (HFM-99)
1401 Rockville Pike
Rockville, MD 20852-1448

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Alcon
RESEARCH, Ltd.

July 8, 2008

6201 South Freeway
Fort Worth, Texas 76134-2099
(817) 293-0450

Mr. Gary Buehler
Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place
Rockville, MD 20855-2773

Sarah Cantrell, M.A. R7-18
Asst. Director, Regulatory Affairs
6201 South Freeway
Ft. Worth, Texas 76134-2099

Re: **ANDA 77-200**
Ketotifen Fumarate Ophthalmic Solution, 0.025%
TELEPHONE AMENDMENT: (b) (4) Information

Dear Mr. Buehler:

Alcon is providing the (b) (4) information for ANDA 77-200, Ketotifen Fumarate Ophthalmic Solution, 0.025% as requested by Roslyn Adigun, Project Manager on July 2, 2008. This information demonstrates compliance with (b) (4)

Alcon, Inc. has previously submitted a Letter of Non-Repudiation.

We appreciate the Agency's time and consideration spent in the review of this application. If there are any questions, regarding the content or format of this application, do not hesitate to contact the undersigned directly at (817) 551-4517 or via facsimile to (817) 551-4630

Sincerely,

Sarah Cantrell

Sarah J. Cantrell, MA
Assistant Director, Regulatory Affairs

Enclosure

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: September 30, 2008
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FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Alcon, Inc.	July 8, 2008
TELEPHONE NO. *(Include Area Code)*	FACSIMILE *(FAX)* Number *(Include Area Code)*
817-551-8568	817-551-4630
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued)*:	AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE
P.O. Box 62 Bosch 69 CH-6331, Hunenberg Switzerland	Alcon Research, Ltd. R7-18 Phone: 817-551-8568 6201 South Freeway Fax: 817-551-4630 Fort Worth, Texas 76134-0450

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* **77-200**

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Ketotifen Fumerate Ophthalmic Solution	

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*	CODE NAME *(If any)*

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Solution	0.025%	Topical, ocular

(PROPOSED) INDICATION(S) FOR USE:
Temporarily relieves itchy eyes due to pollen, ragweed, grass, animal hair and dander.

APPLICATION DESCRIPTION

APPLICATION TYPE *(check one)* ☐ NEW DRUG APPLICATION (CDA, 21 CFR 314.50) ☒ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94) ☐ BIOLOGICS LICENSE APPLICATION (BLA, 21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☐505 (b)(1) ☐ 505 (b)(2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug Zaditor Holder of Approved Application Novartis

TYPE OF SUBMISSION *(check one)* ☐ ORIGINAL APPLICATION ☒ AMENDMENT TO APENDING APPLICATION ☐ RESUBMISSION ☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION
Telephone Amendment: (b) (4) Information

PROPOSED MARKETING STATUS *(check one)* ☐ PRESCRIPTION PRODUCT (Rx) ☒ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 THIS APPLICATION IS ☐ PAPER ☒ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

This application contains the following items: *(Check all that apply)*	
☐	1 Index
☐	2. Labeling *(check one)* ☐ Draft Labeling ☒ Final Printed Labeling
☐	3. Summary (21 CFR 314.50 (c))
☒	4. Chemistry section
☒	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
☐	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
☐	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
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☐	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
☐	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
☐	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
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☐	18. User Fee Cover Sheet (Form FDA 3397)
☐	19. Financial Information (21 CFR Part 54)
☐	20. OTHER *(Specify)*

CERTIFICATION

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1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
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3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE:
Sarah Cantrell	Sarah Cantrell, Asst. Director, Regulatory Affairs	7/8/08

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
6201 South Freeway, Fort Worth, Texas 76134-2099	(817) 551-4517

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research (HFM-99)
1401 Rockville Pike
Rockville, MD 20852-1448

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Response to

FDA
(Issue of 01 July 2008)

on

Ketotifen Fumarate Ophthalmic Solution, 0.025%

ISSUE 1:

Please provide documentation for Ketotifen Fumarate Ophthalmic Solution, 0.025% that demonstrates compliance of the drug substance, excipients and drug product with (b) (4)

RESPONSE:

(b) (4)

Tab 1

11 pages are withheld immediately following this page as b4

June 11, 2008

Alcon RESEARCH, Ltd.

Mr. Gary Buehler
Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place
Rockville, MD 20855-2773

6201 South Freeway
Fort Worth, Texas 76134-2099
(817) 293-0450
Sarah Cantrell, M.A. R7-18
Asst. Director, Regulatory Affairs
6201 South Freeway
Ft. Worth, Texas 76134-2099

Re: **ANDA 77-200**
Ketotifen Fumarate Ophthalmic Solution, 0.025%
Amendment: Withdrawal of (b) (4) Request

Dear Mr. Buehler:

Alcon is withdrawing the request for (b) (4)

As appropriate, communications may be sent via facsimile to (817) 551-4630. If there are any questions, regarding the content or format of this application, do not hesitate to contact the undersigned directly at (817) 551-4517.

Sincerely,

Sarah Cantrell

Sarah J. Cantrell, MA
Assistant Director, Regulatory Affairs

Enclosure

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: September 30, 2008
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Alcon, Inc.	June 11, 2008
TELEPHONE NO. *(Include Area Code)*	**FACSIMILE** *(FAX)* **Number** *(Include Area Code)*
817-551-8568	817-551-4630
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):* P.O. Box 62 Bosch 69 CH-6331, Hunenberg Switzerland	**AUTHORIZED U.S. AGENT NAME & ADDRESS** *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE Alcon Research, Ltd. R7-18 Phone: 817-551-8568 6201 South Freeway Fax: 817-551-4630 Fort Worth, Texas 76134-0450

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* **77-200**

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Ketotifen Fumerate Ophthalmic Solution	

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*

CODE NAME *(If any)*

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Solution	0.025%	Topical, ocular

(PROPOSED) INDICATION(S) FOR USE:
Temporarily relieves itchy eyes due to pollen, ragweed, grass, animal hair and dander.

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APPLICATION TYPE *(check one)* ☐ NEW DRUG APPLICATION (CDA, 21 CFR 314.50) ☒ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94)
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IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug Zaditor Holder of Approved Application Novartis

TYPE OF SUBMISSION *(check one)* ☐ ORIGINAL APPLICATION ☒ AMENDMENT TO APENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT
☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION
Withdrawal of [redacted] (b) (4)

PROPOSED MARKETING STATUS *(check one)* ☐ PRESCRIPTION PRODUCT (Rx) ☒ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 THIS APPLICATION IS ☐ PAPER ☒ PAPER AND ELECTRONIC ☐ ELECTRONIC

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☐	18. User Fee Cover Sheet (Form FDA 3397)
☐	19. Financial Information (21 CFR Part 54)
☒	20. OTHER *(Specify)* Withdrawal of Trade Name Request

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

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2. Biological establishment standards in 21 CFR Part 600.
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4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
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6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

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SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
Sarah Cantrell	Sarah Cantrell, Asst. Director, Regulatory Affairs	6/11/08

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
6201 South Freeway, Fort Worth, Texas 76134-2099	(817) 551-4517

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Rockville, MD 20852-1448

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June 11, 2008

Alcon RESEARCH, Ltd.

6201 South Freeway
Fort Worth, Texas 76134-2099
(817) 293-0450

Sarah Cantrell, M.A. R7-18
Asst. Director, Regulatory Affairs
6201 South Freeway
Ft. Worth, Texas 76134-2099

Mr. Gary Buehler
Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place
Rockville, MD 20855-2773

Re: **ANDA 77-200**
Ketotifen Fumarate Ophthalmic Solution, 0.025%
Telephone Amendment: OTC Labeling

Dear Mr. Buehler:

As requested, Alcon is providing the OTC labeling for Ketotifen Fumarate Ophthalmic Solution, 0.025% since the reference listed drug (RLD) upon which we based our application, Zaditor, has changed status from Rx to OTC.

Alcon is providing a CD containing a proposed OTC container label and carton for Ketotifen Fumarate Ophthalmic Solution, RLD labeling and annotated labeling comparing the RLD to proposed labeling

We appreciate the Agency's time and consideration spent in the review of this application and especially the assistance of Postelle Birch-Smith. As appropriate, communications may be sent via facsimile to (817) 551-4630. If there are any questions, regarding the content or format of this application, do not hesitate to contact the undersigned directly at (817) 551-4517.

Sincerely,

Sarah Cantrell

Sarah J. Cantrell, MA
Assistant Director, Regulatory Affairs

Enclosures

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: September 30, 2008
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Alcon, Inc.	June 11, 2008
TELEPHONE NO. *(Include Area Code)*	**FACSIMILE** *(FAX)* **Number** *(Include Area Code)*
817-551-8568	817-551-4630
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):*	**AUTHORIZED U.S. AGENT NAME & ADDRESS** *(Number, Street, City, State, ZIP Code, telephone & FAX number)* **IF APPLICABLE**
P.O. Box 62 Bosch 69 CH-6331, Hunenberg Switzerland	Alcon Research, Ltd. R7-18 Phone: 817-551-8568 6201 South Freeway Fax: 817-551-4630 Fort Worth, Texas 76134-0450

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* **77-200**

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
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CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*

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Solution	0.025%	Topical, ocular

(PROPOSED) INDICATION(S) FOR USE:
Temporarily relieves itchy eyes due to pollen, ragweed, grass, animal hair and dander.

APPLICATION DESCRIPTION

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Name of Drug Zaditor Holder of Approved Application Novartis

TYPE OF SUBMISSION *(check one)* ☐ ORIGINAL APPLICATION ☒ AMENDMENT TO APENDING APPLICATION ☐ RESUBMISSION ☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION
Telephone Amendment: OTC Labeling Revisions

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☐	19. Financial Information (21 CFR Part 54)
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Sarah Cantrell	Sarah Cantrell, Asst. Director, Regulatory Affairs	6/11/08

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1401 Rockville Pike
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April 7, 2008

Alcon RESEARCH, Ltd.

6201 South Freeway
Fort Worth, Texas 76134-2099
(817) 293-0450

Mr. Gary Buehler
Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place
Rockville, MD 20855-2773

Re: **ANDA 77-200**
Ketotifen Fumarate Ophthalmic Solution, 0.025%
MINOR AMENDMENT: FINAL APPROVAL REQUESTED

Dear Mr. Buehler:

Alcon is requesting final approval for ANDA 77-200, Ketotifen Fumarate Ophthalmic Solution, 0.025%. There are no changes in the chemistry, manufacturing and controls data as previously provided.

On March 24, 2008, OTC labeling for Ketotifen Fumarate Ophthalmic Solution, 0.025% was submitted since the reference listed drug (RLD) upon which we based our application, Zaditor, changed status from Rx to OTC. At that time, (b) (4) [redacted] We understand that this review is ongoing.

Alcon, Inc. has previously submitted a Letter of Non-Repudiation.

We appreciate the Agency's time and consideration spent in the review of this application. If there are any questions, regarding the content or format of this application, do not hesitate to contact the undersigned directly at (817) 551-4517 or via facsimile to (817) 551-4630

Sincerely,

Sarah Cantrell

Sarah J. Cantrell, MA
Assistant Director, Regulatory Affairs

Enclosure

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: September 30, 2008
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Alcon, Inc.	April 7, 2008
TELEPHONE NO. *(Include Area Code)*	**FACSIMILE** *(FAX)* **Number** *(Include Area Code)*
817-551-8568	817-551-4630
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):*	**AUTHORIZED U.S. AGENT NAME & ADDRESS** *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE
P.O. Box 62 Bosch 69 CH-6331, Hunenberg Switzerland	Alcon Research, Ltd. R7-18 Phone: 817-551-8568 6201 South Freeway Fax: 817-551-4630 Fort Worth, Texas 76134-0450

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* **77-200**

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Ketotifen Fumerate Ophthalmic Solution	(b) (4)

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*

CODE NAME *(If any)*

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Solution	0.025%	Topical, ocular

(PROPOSED) INDICATION(S) FOR USE:
Temporarily relieves itchy eyes due to pollen, ragweed, grass, animal hair and dander.

APPLICATION DESCRIPTION

APPLICATION TYPE *(check one)* ☐ NEW DRUG APPLICATION (CDA, 21 CFR 314.50) ☒ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94) ☐ BIOLOGICS LICENSE APPLICATION (BLA, 21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☐505 (b)(1) ☐ 505 (b)(2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

Name of Drug Zaditor Holder of Approved Application Novartis

TYPE OF SUBMISSION *(check one)* ☐ ORIGINAL APPLICATION ☒ AMENDMENT TO APENDING APPLICATION ☐ RESUBMISSION ☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION
Minor Amendment: Final Approval Requested

PROPOSED MARKETING STATUS *(check one)* ☐ PRESCRIPTION PRODUCT (Rx) ☒ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 THIS APPLICATION IS ☐ PAPER ☒ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

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This application contains the following items: *(Check all that apply)*	
☐	1. Index
☐	2. Labeling *(check one)* ☐ Draft Labeling ☐ Final Printed Labeling
☐	3. Summary (21 CFR 314.50 (c))
☐	4. Chemistry section
☐	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
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☐	18. User Fee Cover Sheet (Form FDA 3397)
☐	19. Financial Information (21 CFR Part 54)
☒	20. OTHER *(Specify)* Final Approval Requested

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

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3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE:
Sarah Cantrell	Sarah Cantrell, Asst. Director, Regulatory Affairs	4/7/08

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
6201 South Freeway, Fort Worth, Texas 76134-2099	(817) 551-4517

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research (HFM-99)
1401 Rockville Pike
Rockville, MD 20852-1448

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Alcon
RESEARCH, Ltd.

6201 South Freeway
Fort Worth, Texas 76134-2099
(817) 293-0450

March 25, 2008

Mr. Gary Buehler
Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place
Rockville, MD 20855-2773

Re: **ANDA 77-200**
Ketotifen Fumarate Ophthalmic Solution, 0.025%
Amendment: Patent Certification

Dear Mr. Buehler:

Alcon is providing a new patent certification for Ketotifen Fumarate Ophthalmic Solution, 0.025% since the reference listed drug (RLD) upon which we based our application, Zaditor, has changed status from Rx to OTC. Since the patents are no longer listed in the Orange Book, Alcon is providing a Paragraph I Certification.

We apprcciate the Agency's time and consideration spent in the review of this application. As appropriate, communications may be sent via facsimile to (817) 551-4630. If there are any questions, regarding the content or format of this application, do not hesitate to contact the undersigned directly at (817) 551-4517.

Sincerely,

Sarah Cantrell

Sarah J. Cantrell, MA
Assistant Director, Regulatory Affairs

Enclosures

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

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Expiration Date: September 30, 2008
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APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Alcon, Inc.	March 25, 2008
TELEPHONE NO. *(Include Area Code)*	FACSIMILE *(FAX)* Number *(Include Area Code)*
817-551-8568	817-551-4630
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued)*:	AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE
P.O. Box 62 Bosch 69 CH-6331, Hunenberg Switzerland	Alcon Research, Ltd. R7-18 Phone: 817-551-8568 6201 South Freeway Fax: 817-551-4630 Fort Worth, Texas 76134-0450

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)*

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
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If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

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SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE:
Sarah Cantrell	Sarah Cantrell, Asst. Director, Regulatory Affairs	3/25/08

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
6201 South Freeway, Fort Worth, Texas 76134-2099	(817) 551-4517

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Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

Department of Health and Human Services
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Center for Biologics Evaluation and Research (HFM-99)
1401 Rockville Pike
Rockville, MD 20852-1448

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PATENT CERTIFICATION

Paragraph I Certification

In accordance with the Federal Food, Drug and Cosmetic Act, Patent Certification is hereby provided for Alcon, Inc.'s Abbreviated New Drug Application for Ketotifen Fumarate Ophthalmic Solution, 0.025%.

Alcon, Inc. hereby certifies that, in its opinion and to the best of its knowledge, there are no patents listed in the FDA's Orange Book for Zaditor (ketotifen fumarate), the reference listed drug. This certification is made in accordance with Section 505(j)(2)(A)(vii)(I) of Title 1 of the Federal Food, Drug, and Cosmetic Act, and pursuant to 21 CFR 314.94(a)(12)(i)(A)(1).

On behalf of
Alcon, Inc.

Patrick M. Ryan

9/14/07
Date

March 24, 2008

Alcon RESEARCH, Ltd.

6201 South Freeway
Fort Worth, Texas 76134-2099
(817) 293-0450

Mr. Gary Buehler
Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place
Rockville, MD 20855-2773

Re: **ANDA 77-200**
Ketotifen Fumarate Ophthalmic Solution, 0.025%
Amendment: OTC Labeling for [redacted] (b) (4)

Dear Mr. Buehler:

As requested, Alcon is providing the OTC labeling for Ketotifen Fumarate Ophthalmic Solution, 0.025% since the reference listed drug (RLD) upon which we based our application, Zaditor, has changed status from Rx to OTC. In addition to review of the OTC labeling content, Alcon is requesting formal review [redacted] (b) (4)

[redacted] at the same time as Alcon has a pending ANDA approval.

Alcon is providing a CD containing a folder for [redacted] (b) (4)

[redacted]

labeling

If an additional CD containing this labeling will be useful for the Division of Medication Errors and Technical Support in their review of [redacted] (b) (4), then please contact me and I will be happy to provide another copy.

We appreciate the Agency's time and consideration spent in the review of this application. As appropriate, communications may be sent via facsimile to (817) 551-4630. If there are any questions, regarding the content or format of this application, do not hesitate to contact the undersigned directly at (817) 551-4517.

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REASON FOR SUBMISSION
Amendment: OTC Labeling (b) (4)

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Sarah Cantrell	Sarah Cantrell, Asst. Director, Regulatory Affairs	3/24/08

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
6201 South Freeway R7-18 Fort Worth, Texas 76134-2099	(817) 551-4517

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research (HFM-99)
1401 Rockville Pike
Rockville, MD 20852-1448

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Alcon
RESEARCH, Ltd.

6201 South Freeway
Fort Worth, Texas 76134-2099
(817) 293-0450

March 25, 2008

Mr. Gary Buehler
Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place
Rockville, MD 20855-2773

ORIG AMENDMENT
N-000-XP

NAI
gm 5/6/08

Re: **ANDA 77-200**
Ketotifen Fumarate Ophthalmic Solution, 0.025%
Amendment: Patent Certification

Dear Mr. Buehler:

Alcon is providing a new patent certification for Ketotifen Fumarate Ophthalmic Solution, 0.025% since the reference listed drug (RLD) upon which we based our application, Zaditor, has changed status from Rx to OTC. Since the patents are no longer listed in the Orange Book, Alcon is providing a Paragraph I Certification.

We appreciate the Agency's time and consideration spent in the review of this application. As appropriate, communications may be sent via facsimile to (817) 551-4630. If there are any questions, regarding the content or format of this application, do not hesitate to contact the undersigned directly at (817) 551-4517.

Sincerely,

Sarah Cantrell

Sarah J. Cantrell, MA
Assistant Director, Regulatory Affairs

Enclosures

RECEIVED
MAR 26 2008
OGD

March 24, 2008

Alcon
RESEARCH, Ltd.

6201 South Freeway
Fort Worth, Texas 76134-2099
(817) 293-0450

Mr. Gary Buehler
Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place
Rockville, MD 20855-2773

ORIG AMENDMENT
N-AF

Re: **ANDA 77-200**
Ketotifen Fumarate Ophthalmic Solution, 0.025%
Amendment: OTC Labeling for (b) (4)

Dear Mr. Buehler:

As requested, Alcon is providing the OTC labeling for Ketotifen Fumarate Ophthalmic Solution, 0.025% since the reference listed drug (RLD) upon which we based our application, Zaditor, has changed status from Rx to OTC. In addition to review of the OTC labeling content, Alcon is requesting (b) (4)

(b) (4)

MAR 25 2008

OGD

If an additional CD containing this labeling will be useful for the Division of Medication Errors and Technical Support in their review of [redacted] (b) (4), then please contact me and I will be happy to provide another copy.

We appreciate the Agency's time and consideration spent in the review of this application. As appropriate, communications may be sent via facsimile to (817) 551-4630. If there are any questions, regarding the content or format of this application, do not hesitate to contact the undersigned directly at (817) 551-4517.

Sincerely,

Sarah Cantrell

Sarah J. Cantrell, MA
Assistant Director, Regulatory Affairs

Enclosures

OGD APPROVAL ROUTING SUMMARY

ANDA # 77-200 Applicant Alcon, Inc.
Drug Kerotifen Fumarate Opthalmic Solution Strength(s) 0.025%

APPROVAL ☐ TENTATIVE APPROVAL X SUPPLEMENTAL APPROVAL (NEW STRENGTH) ☐ OTHER ☐

REVIEWER:	DRAFT Package	FINAL Package
1. Martin Shimer Chief, Reg. Support Branch	Date 20 Jan 06 Initials MS	Date Initials

Contains GDEA certification: (Yes) No (required if sub after 6/1/92)
Determ. of Involvement? Yes No
Pediatric Exclusivity System
RLD = NDA#
Patent/Exclusivity Certification: (Yes) No
Date Checked
If Para. IV Certification- did applicant
Nothing Submitted
Notify patent holder/NDA holder Yes No
Written request issued
Was applicant sued w/in 45 days: Yes No
Study Submitted
Has case been settled: Yes No Date settled:
Is applicant eligible for 180 day
Generic Drugs Exclusivity for each strength: Yes (No)
Date of latest Labeling Review/Approval Summary 5/5/2005
Any filing status changes requiring addition Labeling Review Yes ☐ No ☐
Type of Letter: PIII to '137, '982 & '409 All exp 1/13/2019
Comments: Eligible for TA only

2. Project Manager, Rosalyn Adigun Team 3 Review Support Branch	Date R 01/20/06 Initials RA	Date Initials

Original Rec'd date 07/01/04
Date Acceptable for Filing 07/02/04
Patent Certification (type) III
Date Patent/Exclus.expires 01/13/19
Citizens' Petition/Legal Case Yes (No)
(If YES, attach email from PM to CP coord)
First Generic (Yes) No

EER Status Pending (Acceptable) OAI
Date of EER Status 08/31/04
Date of Office Bio Review 04/21/05
Date of Labeling Approv. Sum 05/04/05
Labeling Acceptable Email Rec'd Yes ☐ No ☐
Labeling Acceptable Email filed Yes ☐ No ☐
Date of Sterility Assur. App. 5/11/05
Methods Val. Samples (Pending) Yes No
MV Commitment Rcd. from Firm Yes No

Acceptable Bio reviews tabbed (Yes) No
Suitability Petition/Pediatric Waiver
Modified-release dosage form: Yes (No)
Interim Dissol. Specs in AP Ltr: Yes
Pediatric Waiver Request Accepted Rejected Pending
Previously reviewed and tentatively approved Date
Previously reviewed and CGMP def. /NA Minor issued Date
Comments:

3. David Read **(PP IVs Only)** Pre-MMA Language included OGD Regulatory Counsel, Post-MMA Language Included Comments:	Date Initials

4. Div. Dir./Deputy Dir. Chemistry Div. I II OR III Comments:	Date 3/1/06 Initials PS

CMC OK
impurities are controlled

2019

REVIEWER: **FINAL ACTION**

5. Frank Holcombe **First Generics Only** Date 3/17/06
Assoc. Dir. For Chemistry Initials RR
Comments: (First generic drug review) For Frank;

Cmc acceptable, [redacted] (b) (4) 3/17/06

6. Vacant Date _____
Deputy Dir., DLPS Initials _____

7. Peter Rickman Date 3/17/2006
Director, DLPS Initials
Para.IV Patent Cert: Yes No ;Pending Legal Action: Yes No ;Petition: Yes No
Comments:
PIII to the '137, '982 & '429 patents all patents expire 1/13/2019
No w/H ex clusivity
OK for TA only

OR

Bio acceptable 4/21/2005 (waiver granted)
Labeling acceptable 5/5/2005 per AP Labeling Summary
EER acceptable 8/10/2004
micro acceptable 5/11/2005 TA only

8. Robert L. West Date _____
Deputy Director, OGD Initials _____
Para.IV Patent Cert: Yes No ; Pending Legal Action: Yes No ; Petition: Yes No
Comments:

9. Gary Buehler Date 3/17/06
Director, OGD Initials GS
Comments:
First Generic Approval PD or Clinical for BE Special Scientific or Reg.Issue

10. Project Manager, Team 3 Date 3/20/06
Review Support Branch Initials
3/20 Date PETS checked for first generic drug (just prior to notification to firm)
Applicant notification:
3/20 8:18AM Time notified of approval by phone 3/20 8:20 AM Time approval letter faxed
FDA Notification:
3/20 Date e-mail message sent to "CDER-OGDAPPROVALS" distribution list.
3/20 Date Approval letter copied to \\CDS014\DRUGAPP\ directory.

File V:/division/dlps/approvrou9.doc

Alcon
RESEARCH, Ltd.

6201 SOUTH FREEWAY
FORT WORTH, TEXAS 76134-2099
(817) 293-0450

ORIG AMENDMENT
N / Am

RECEIVED
MAR 0 1 2006
OGD / CDER

February 28, 2006

Mr. Gary Buehler
Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2273

RE: **ANDA 77-200 KETOTIFEN FUMARATE OPHTHALMIC SOLUTION**

MINOR TELEPHONE AMENDMENT OF FEBRUARY 16, 2006

Dear Mr. Buehler:

Please find enclosed response to the telephone request of February 16, 2006 to monitor [redacted] (b) (4) Impurities. Alcon's test methods detect each of the listed impurities, and they will be monitored in each incoming lot of drug substance. Alcon has already validated this method and results data (also included in the ANDA submission) is included.

If you require additional information, please contact me at 817-551-8568.

Sincerely,

Norma J. Schafer

Norma J. Schafer
Regulatory Affairs

Alcon
RESEARCH, Ltd.

6201 SOUTH FREEWAY
FORT WORTH, TEXAS 76134-2099
(817) 293-0450

N/AM

February 24, 2006

TO: Dr. Laing Lee Huang
301-594-0180

FROM: Norma Schafer
(817) 551-8568

RE: **ANDA 77-200 KETOTIFEN FUMARATE OPHTHALMIC SOLUTION**

MINOR TELEPHONE AMENDMENT OF FEBRUARY 16, 2006

Dr. Huang, please find enclosed commitment concerning the request to monitor [redacted] (b) (4) Impurities. Alcon's test methods do detect each of the listed impurities and will be monitored in each incoming lot of drug substance. Alcon has already validated this method and results data (also included in the ANDA submission) is included.

Please confirm that this meets your expectation. I will submit a paper copy, once I have confirmation that we meet your expectations.

Alcon
RESEARCH, Ltd.

6201 SOUTH FREEWAY
FORT WORTH, TEXAS 76134-2099
(817) 293-0450

February 24, 2006

TO: Dr. Laing Lee Huang
301-594-0180

FROM: Norma Schafer

RE: **ANDA 77-200 Ketotifen Fumarate Ophthalmic Solution**

MINOR TELEPHONE AMENDMENT OF FEBRUARY 16, 2006

Dr. Huang, please find enclosed commitment to add [redacted] (b) (4) Impurity Specifications. We have grouped them to be monitored and controlled by the specification of NMT [redacted] (b) (4) % for Any Individual Impurity.

Please let me know if meets your expectation or if you would prefer the format listed below.

[redacted] (b) (4)

Norma Schafer
(817) 551-8568

ORIG AMENDMENT

N|AM

Alcon
RESEARCH, Ltd.

6201 SOUTH FREEWAY
FORT WORTH, TEXAS 76134-2099
(817) 293-0450

October 26, 2005

Mr. Gary Buehler
Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place
Rockville, MD 20855-2773

Re: **ANDA 77-200 Ketotifen Fumarate Ophthalmic Solution, 0.025%**
MINOR Amendment to Application

Dear Mr. Buehler:

Alcon, Inc. is submitting a response to the FDA request of August 5, 2005.

Please find enclosed one review copy and one archive copy of the responses plus two bound copies of the analytical methods, method validation and data, as requested. Since of the methods have had minor updates, an archive copy is being provided.

A field copy has been sent to the Dallas office.

If there are any questions, do not hesitate to contact the undersigned directly at (817) 551-8568.

Sincerely,

Norma J. Schafer

Norma J. Schafer
Regulatory Affairs, Manager

Enclosures

Alcon
RESEARCH, Ltd.

6201 SOUTH FREEWAY
FORT WORTH, TEXAS 76134-2099
(817) 293-0450

August 5, 2005

Mc

Mr. Gary Buehler
Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2273

Re: **ANDA 77-200 Ketotifen Fumarate Ophthalmic Solution, 0.025%**

INTENT TO AMEND

Dear Mr. Buehler:

Reference is made to your letter dated August 5, 2005, received at Alcon on August 5, 2005, regarding our application for a new drug product. Pursuant to the conditions outlined under 21 CFR 314.120(a)(1), please be advised that Alcon intends to file an amendment to the pending application.

If you require additional information, please contact me at 817-551-8568.

Sincerely,

Norma J. Schafer
Regulatory Affairs

ORIG AMENDMENT
N/AF

Alcon
RESEARCH, Ltd.

6201 South Freeway
Fort Worth, Texas 76134-2099
(817) 293-0450

April 7, 2005

Mr. Gary Buehler
Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place
Rockville, MD 20855-2773

Re: **ANDA 77-200 Ketotifen Fumarate Ophthalmic Solution, 0.025%**
Amendment to Application

Dear Mr. Buehler:

Please find enclosed Alcon's response to the FDA request of March 3, 2005 for an updated container label and patent certification. A copy of the amendment letter, the 356h, the container Final Printed Label, the Annotated Label and the certification are included on the CD. A paper copy of the amendment letter, the 356h, the container Final Printed Label and the certification are also included. No Carton or Insert labeling is provided since they are noted in the review as "Satisfactory in Final Printed Labeling."

Please find enclosed two review copies and one archive copy of this amendment submission. A field copy has been sent to the Dallas office.

If there are any questions, do not hesitate to contact the undersigned directly at (817) 551-8568.

Sincerely,

Norma J. Schafer
Regulatory Affairs

Enclosures

RECEIVED
APR 08 2005
OGD/CDER

Alcon
RESEARCH, Ltd.

6201 South Freeway
Fort Worth, Texas 76134-2099
(817) 293-0450

February 15, 2005

Mr. Gary Buehler
Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place
Rockville, MD 20855-2773

ORIG AMENDMENT
N/A m

Re: **ANDA 77-200 Ketotifen Fumarate Ophthalmic Solution, 0.025%**
Amendment to Application

Dear Mr. Buehler:

Alcon, Inc. is submitting a response to the FDA request of November 15, 2004.

Please find enclosed two review copies and one archive copy of this amendment submission. A field copy has been sent to the Dallas office.

If there are any questions, do not hesitate to contact the undersigned directly at (817) 551-8568.

Sincerely,

Norma J. Schafer

Norma J. Schafer
Regulatory Affairs

Enclosures

Alcon
RESEARCH, Ltd.

6201 South Freeway
Fort Worth, Texas 76134-2099
(817) 293-0450

November 16, 2004

NIMC

MHT
11/23/04

Mr. Gary Buehler
Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2273

Re: **ANDA 77-200 Ketotifen Fumarate Ophthalmic Solution, 0.025%**
INTENT TO AMEND

Dear Mr. Buehler:

Reference is made to your letter dated November 15, 2004, received at Alcon on November 15, 2004, regarding our application for a new ANDA for Ketotifen Fumarate Ophthalmic Solution, 0.025%. Pursuant to the conditions outlined under 21 CFR 314.110(a)(1), please be advised that Alcon intends to file an amendment to the pending supplement.

If you require additional information, please contact me at 817-551-8568.

Sincerely,

Norma J. Schafer
Regulatory Affairs

ANDA CHECKLIST
FOR COMPLETENESS and ACCEPTABILITY of an APPLICATION

ANDA Nbr: 77-200 **FIRM NAME**: ALCON INC.

RELATED APPLICATION(S): NA

First Generic Product Received? YES

DRUG NAME: KETOTIFEN FUMARATE
DOSAGE FORM: OPHTHALMIC SOLUTION, 0.025%

Bio Assignments:	☒ Micro Review
☒ BPH	
☐ BCE	
☐ BST	

Random Queue: 3
Chem Team Leader: Fan, James PM: Ann Vu Labeling Reviewer: Beverly Weitzman

Letter Date: JULY 01, 2004	**Received Date**: JULY 02, 2004
Comments: EC- 1 YES	**On Cards:** YES
Therapeutic Code: 9000000 ANTHISTAMINE	
Archival Format: PAPER	**Sections** I **(356H Sections per EDR Email)**
Review copy: YES Not applicable to electronic sections	E-Media Disposition: NA
Field Copy Certification (Original Signature) YES	
Methods Validation Package (3 copies PAPER archive) (Required for Non-USP drugs)	**NO**
Cover Letter YES	**Table of Contents** YES
PART 3 Combination Product Category (Must be completed for ALL Original Applications)	N Not a Part3 Combo Product Refer to the Part 3 Combination Algorithm

Reviewing CSO/CST **Jeen Min** **Date** 8/26/04	**Recommendation:** ☒ **FILE** ☐ **REFUSE to RECEIVE**
Supervisory Concurrence/Date:	**Date:** 27 Aug 2004
ADDITIONAL COMMENTS REGARDING THE ANDA:	
Top 200 Drug Product:	

ACCEPTABLE

Sec. I	**Signed and Completed Application Form (356h)** YES (Statement regarding Rx/OTC Status) RX YES	☒
Sec. II	**Basis for Submission** **NDA# : 21-066** YES Ref Listed Drug: ZADITOR Firm: NOVARTIS ANDA suitability petition required? NO If Yes, then is change subject to PREA (change in dosage form, route, active ingredient) For products subject to PREA a wavier request must be granted prior to approval of ANDA. Wavier Granted:	☒
Sec. III	**Patent Certification** 1. Paragraph: I YES 2. Expiration of Patent: NA A. Pediatric Exclusivity Submitted? B. Pediatric Exclusivity Tracking System checked? **Exclusivity Statement:** Yes (See Section 3.A.10)	☒
Sec. IV	**Comparison between Generic Drug and RLD-505(j)(2)(A)** 1. Conditions of use YES Do not specifically state but will accept labeling comparison. 2. Active ingredients YES 3. Route of administration YES 4. Dosage Form YES 5. Strength YES	☒
Sec. V	**Labeling** (Mult Copies N/A for E-Submissions) 1. 4 copies of draft (each strength and container) or 12 copies of FPL YES 2. 1 RLD label and 1 RLD container label YES 3. 1 side by side labeling comparison with all differences annotated and explained YES 4. Was a proprietary name request submitted? NO (If yes, send email to Labeling Rvwr indicating such.) *(ELECTRONIC LABELING IS REQUIRED AS OF JUNE 8 but Labeling Division will accept the paper format but said that the electronic PI will be needed for approval.)*	☒
Sec. VI	**Bioavailability/Bioequivalence** **1. Financial Certification** (Form FDA 3454) **and Disclosure Statement** (Form 3455) NO **2. Request for Waiver of In-Vivo Study(ies): YES** **3. Formulation data same?** (Comparison of all Strengths) (Ophthalmics, Otics, Topicals Perenterals) YES (SEE SECTION 2.3.P.1) **4. Lot Numbers of Products used in BE Study(ies):** N/A **5. Study Type: IN-VIVO PK STUDY(IES)** (Continue with the appropriate study type box below)	☒

Study Type	**IN-VIVO PK STUDY(IES)** (i.e., fasting/fed/sprinkle) NA a. Study(ies) meets BE criteria (90% CI or 80-125, Cmax, AUC) b. EDR Email: Data Files Submitted: NO c. In-Vitro Dissolution: NO	☐
Study Type	**IN-VIVO BE STUDY with CLINICAL ENDPOINTS** NO a. Properly defined BE endpoints (eval. by Clinical Team) b. Summary results meet BE criteria (90% CI within +/- 20% or 80-120) c. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo ($p<0.05$) (eval. by Clinical Team) d. EDR Email: Data Files Submitted	☐
Study Type	**TRANSDERMAL DELIVERY SYSTEMS** NO a. <u>In-Vivo PK Study</u> 1. Study(ies) meet BE Criteria (90% CI or 80-125, Cmax, AUC) 2. In-Vitro Dissolution 3. EDR Email: Data Files Submitted b. <u>Adhesion Study</u> c. <u>Skin Irritation/Sensitization Study</u>	☐
Study Type	**NASALLY ADMINISTERED DRUG PRODUCTS** NO a. <u>Solutions</u> (Q1/Q2 sameness): 1. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming, Tail Off Profile) b. <u>Suspensions</u> (Q1/Q2 sameness): 1. In-Vivo PK Study a. Study(ies) meets BE Criteria (90% CI or 80-125, Cmax, AUC) b. EDR Email: Data Files Submitted 2. In-Vivo BE Study with Clinical EndPoints a. Properly defined BE endpoints (eval. by Clinical Team) b. Summary results meet BE criteria (90% CI within +/- 20% or 80-120) c. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo ($p<0.05$) (eval. by Clinical Team) d. EDR Email: Data Files Submitted 3. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming, Tail Off Profile)	☐
Study Type	**TOPICAL CORTICOSTEROIDS (VASOCONSTRICTOR STUDIES)** NO a. Pilot Study (determination of ED50) b. Pivotal Study (study meets BE criteria 90%CI or 80-125)	☐
Sec. VII	**Components and Composition Statements** 1. Unit composition and batch formulation YES (SEE SECTION 2.3.P.1) 2. Inactive ingredients as appropriate YES All excepients are acceptable as per IIG and FILING REGULATIONS.	☒

Sec. VIII	**Raw Materials Controls** 1. **Active Ingredients** a. Addresses of bulk manufacturers YES (SEE SECTION 2.3.S.2) b. Type II DMF authorization letters or synthesis DMF # (b) (4) c. COA(s) specifications and test results from drug substance mfgr(s) YES (SEE 3.2.S.4.4) d. Applicant certificate of analysis YES (SEE 3.2.S.4.4) e. Testing specifications and data from drug product manufacturer(s) YES (SEE 3.2.S.4) f. Spectra and chromatograms for reference standards and test samples YES (SEE 3.2.P.5.2-1) g. CFN numbers 2. **Inactive Ingredients** a. Source of inactive ingredients identified YES (SEE 3.2.P.4) b. Testing specifications (including identification and characterization) YES c. Suppliers' COA (specifications and test results) YES d. Applicant certificate of analysis YES	☒
Sec.IX	**Description of Manufacturing Facility** 1. Full Address(es)of the Facility(ies) YES 2. CGMP Certification: YES (See Tcon Amendment Dated Aug. 25, 2004) 3. CFN numbers (b) (4)	☒
Sec. X	**Outside Firms Including Contract Testing Laboratories** 1. Full Address YES (SEE END OF 356H FORM) 2. Functions YES 3. CGMP Certification/GLP YES (SEE 3.2.P.3.1) 4. CFN numbers	☒
Sec. XI	**Manufacturing and Processing Instructions** 1. Description of the Manufacturing Process (including Microbiological Validation, if Appropriate) YES (SEE 3.2.P.3.3) 2. Master Production Batch Record(s) for largest intended production runs (no more than 10x pilot batch) with equipment specified YES (See Tcon Amendment Dated Aug. 25, 2004 3.If sterile product: Aseptic fill / Terminal sterilization (b) (4) 4.Filter validation (if aseptic fill) 5. Reprocessing Statement YES (SEE 3.2.P.3.3)	☒
Sec. XII	**In-Process Controls** 1. Copy of Executed Batch Record with Equipment Specified, including Packaging Records (Packaging and Labeling Procedures), Batch Reconciliation and Label Reconciliation YES (SEE 3.2.R TAB 1 PAGE 51 VOL. 1.7 AND PAGES 23, 65, 192, 233 VOL. 1.8) 2. In-process Controls - Specifications and data Mrg. Batch No. Batch Size Mfg. Lot No. Batch Size Packaged 65398F (b) (4) (TH) (b) (4) (AC) (b) (4) 65617F (b) (4) (TH) (b) (4) (AC) 65399F (b) (4) (TH) (b) (4) (AC) (b) (4)	☒

Sec. XIII	**Container** 1. Summary of Container/Closure System (if new resin, provide data) YES (SEE 3. 2. P. 7) 2. Components Specification and Test Data (Type III DMF References) YES 3. Packaging Configuration and Sizes YES 4. Container/Closure Testing YES 5. Source of supply and suppliers address YES	☒
Sec. XIV	**Controls for the Finished Dosage Form** 1. Testing Specifications and Data YES 2. Certificate of Analysis for Finished Dosage Form YES (SEE 3. 2. R TAB 3)	☒
Sec. XV	**Stability of Finished Dosage Form** 1. Protocol submitted YES (SEE 3. 2. P. 8) 2. Post Approval Commitments YES 3. Expiration Dating Period (b) (4) YEARS 4. Stability Data Submitted YES a. 3 month accelerated stability data YES b. Batch numbers on stability records the same as the test batch YES	☒
Sec. XVI	**Samples** - Statement of Availability and Identification of: 1. Drug Substance YES (SEE 3. 2. R. 3) 2. Finished Dosage Form YES 3. Same lot numbers YES	☒
Sec. XVII	**Environmental Impact Analysis Statement** YES	☒
Sec. XVIII	**GDEA (Generic Drug Enforcement Act)/Other:** 1. Letter of Authorization (U.S. Agent [if needed, countersignature on 356h]) YES (See Tcon) 2. Debarment Certification (original signature): YES 3. List of Convictions statement (original signature) YES	☒

OGD Template Revised 04/01/2004 /T.Hinchliffe

ANDA 77-200 Final Check List for Branch Chief

✓ 1) Check letter date and stamp date of ANDA vs. drafted letter.

✓ 2) Check for any NC arriving post stamp date but prior to Reg. Review.

✓ 3) Check for gross errors in letter.

✓ 4) Check that correct letter format is used. (PIV vs. Other acknowledgment)

✓ 5) Check address and contact person on letter vs. 356h.

✓ 6) Check for any t-cons and verify date and correspondence date.

✓ 7) Check Patent Certification information in entered in COMIS (by Eda) vs. Actual certification. If multiple patent certifications, should be based on PIV if applicable or latest expiring patent.

✓ 8) Check for any comments or problems raised by reviewer on Check List.

✓ 9) If first generic, copy BE review and file.

✓ 10) Sign Check List.

✓ 11) Check electronic Orange Book to verify current patent information and correct RLD. Zaleska

N/A 12) Check for MOU patents

✓ 13) Review 356h. Check NDA number and RLD for correct reference. If proprietary name proposed, notify Labeling reviewer.

✓ 14) Review Basis for Submission. Zaleska 11-06

✓ 15) Review Patent Certifications and Exclusivity Statement. (If an expiration of an exclusivity has occurred make a note to the Labeling reviewer.

✓ 16) Review Comparison between Generic Drug and RLD for: condition of use, active ingredients, route of administration, dosage form and strength. Check Components and Composition.

✓ 17) Sign cover letter 505 (j)(2)(A) OK, date, and full signature.

✓ 18) Pull USP information. (USP ___yes ✓ no)

✓ 19) Final Grammar review on letter.

✓ 20) Verify information in OGD Patent Tracking System.

✓ 21) EES slip.

✓ 22) Document in record book.

Signature Martin H. Gross date 12 Dec 2006

ORIGINAL

2.1

Alcon
RESEARCH, Ltd.

6201 South Freeway
Fort Worth, Texas 76134-2099
(817) 293-0450

August 25, 2004

Mr. Gary Buehler
Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place
Rockville, MD 20855-2773

MC

Re: ANDA 77-200 Ketotifen Fumarate Ophthalmic Solution, 0.025%
Telephone Amendment per Request of August 18, 2004

Dear Mr. Buehler:

Alcon, Inc. is submitting a telephone amendment per the FDA request of August 18, 2004.

Please find enclosed information as requested.
1) cGMP certificate for ASPEX containing original signatures.
2) Statement of maximum batch size with reference to the original submission.
3) A copy of the Alcon, Inc. transfer of authority to Alcon Research as the U.S. agent.
4) Please find a copy of the exclusivity statement for the reference listed drug in section 3.A.10, page 1.

If there are any questions, do not hesitate to contact the undersigned directly at (817) 551-8568.

Sincerely,

Norma J. Schafer

Norma J. Schafer
Regulatory Affairs

Enclosures

RECEIVED
AUG 26 2004
OGD/CDER

AUG 27 2004

ANDA 77-200

Alcon Research, Ltd.
US Agent for Alcon, Inc.
Attention: Norma Schafer
6201 South Freeway
Fort Worth, TX 76134-2099

Dear Madam:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

Reference is also made to the telephone conversation dated August 18, 2004 and your correspondence dated August 25, 2004.

NAME OF DRUG: Ketotifen Fumarate Ophthalmic Solution, 0.025%

DATE OF APPLICATION: July 1, 2004

DATE (RECEIVED) ACCEPTABLE FOR FILING: July 2, 2004

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Thuyanh (Ann) Vu
Project Manager
301-827-5848

Sincerely yours,

Wm Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 77-200

cc: DUP/Jackets
HFD-600/Division File
Field Copy
HFD-610/
HFD-143/OIM/DRM

Endorsement:
HFD-615/M.Shimer, Chief, RSB _____ date 27 Aug 2004
HFD-615/J.Min, CSO _____ date 8/27/04

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F/T

ANDA Acknowledgment Letter!

Dev. file

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE : July 12, 2004

TO : Director
Division of Bioequivalence (HFD-650)

FROM : Chief, Regulatory Support Branch
Office of Generic Drugs (HFD-615)

SUBJECT: Examination of the bioequivalence study submitted with an ANDA 77-200 for Ketotifen Fumarate Ophthalmic Solution, 0.025% to determine if the application is substantially complete for filing.

Alcon Inc. has submitted ANDA 77-200 for Ketotifen Fumarate Ophthalmic Solution, 0.025%. It is a first generic. In order to accept an ANDA that contains a first generic, the Agency must formally review and make a determination that the application is substantially complete. Included in this review is a determination that the bioequivalence study is complete, and could establish that the product is bioequivalent.

Please evaluate whether the request for study submitted by Alcon Inc. on July 2, 2004 for its Ketotifen Fumarate Ophthalmic product satisfies the statutory requirements of "completeness" so that the ANDA may be filed.

A "complete" bioavailability or bioequivalence study is defined as one that conforms with an appropriate FDA guidance or is reasonable in design and purports to demonstrate that the proposed drug is bioequivalent to the "listed drug".

BIOEQUIVALENCE CHECKLIST
for Application Completeness of First Generic ANDA

ANDA# 77-200 **FIRM NAME** **Alcon Inc.**

DRUG NAME Ketotifen Fumarate

DOSAGE FORM **Ophthalmic Solution,0.025%**
SUBJ: Request for examination of: Completeness

	Summary of Findings by Division of Bioequivalence
☐	**Study meets statutory requirements**
☐	**Study does NOT meet statutory requirements**
	Reason:
X	**Waiver meets statutory requirements**
☐	**Waiver does NOT meet statutory requirements**
	Reason:

RECOMMENDATION: **Acceptable for Filing**

Reviewed by:
Sikta Pradhan
Reviewer
Date: 8/11/04

Kuldeep R. Dhariwal,
Team Leader
Date: 8/11/04

Item Verified:	YES	NO	Information Sent/ Information Required	Comments/ Information to Request
Protocol	☐	☐		N/A
Assay Methodology	☐	☐		N/A
Procedure SOP	☐	☐		N/A
Methods Validation	☐	☐		N/A
Study Results Ln/Lin	☐	☐		N/A
Adverse Events	☐	☐		N/A
IRB Approval	☐	☐		N/A
Dissolution Data	☐	☐		N/A
Pre-screening of Patients	☐	☐		N/A
Chromatograms	☐	☐		N/A
Consent Forms	☐	☐		N/A
Composition	X	☐		
Summary of Study	☐	☐		N/A
Individual Data & Graphs, Linear & Ln	☐	☐		N/A
PK/PD Data Disk Submitted)	☐	☐		N/A
Randomization Schedule	☐	☐		N/A
Protocol Deviations	☐	☐		N/A
Clinical Site	☐	☐		N/A
Analytical Site	☐	☐		N/A

Item Verified:	YES	NO	Information Sent/ Information Required	Comments/ Information to Request
Medical Records	☐	☐		N/A
Clinical Raw Data	☐	☐		N/A
Test Article Inventory	☐	☐		N/A
BIO Batch Size	☐	☐		N/A
Assay of Active Content Drug	☐	☐		
Content Uniformity	☐	☐		N/A
Date of Manufacture	☐	☐		
Exp. Date of RLD	☐	☐		N/A
BioStudy Lot Numbers	☐	☐		N/A
Statistics	☐	☐		N/A
Summary results provided by the firm indicate studies pass BE criteria	☐	☐		N/A
Waiver requests for other strengths / supporting data	☐	☐		N/A

Additional Comments regarding the ANDA:

This is an ophthalmic solution. It contains the same active and inactive ingredients as that of the referenced listed drug, Zaditor^{R}. (NDA #21-066).

Record of Telephone Conversation

The firm was told the following information needs to be submitted to their application:

1. Exclusivity Statements
2. CGMP Certification with original signature.
3. Statement of largest intended production batch.
4. Letter of Authorization for US Agent.

The firm was told that they will have to submit the Package Insert electronically to get their ANDA approved by labeling.

Date:
August 18, 2004

ANDA Number:
77-200

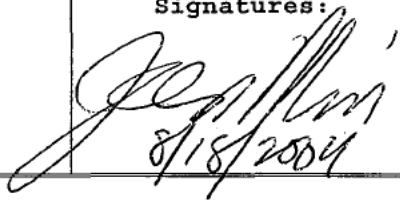
Firm Name:
Alcon

Firm Representative:
Norma Schafer

Phone Number:
817-551-8568

FDA Representative:
Jeen Min

Signatures:



CC: ANDA 77-200

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Alcon
RESEARCH, Ltd.

6201 South Freeway
Fort Worth, Texas 76134-2099
(817) 293-0450

July 1, 2004

Mr. Gary Buehler
Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place
Rockville, MD 20855-2773

Re: Original Submission
Abbreviated New Drug Application
Ketotifen Fumarate Ophthalmic Solution, 0.025%

Dear Mr. Buehler:

Alcon, Inc. is submitting an original abbreviated new drug application (ANDA) seeking approval to market a Ketotifen Fumarate Ophthalmic Solution, 0.025% that is pharmaceutically equivalent to the listed drug, Zaditor Ophthalmic Solution, 0.025% manufactured by Novartis Ophthalmics. Alcon Research, Ltd. is the U.S. representative for Alcon, Inc. This application is submitted pursuant to 505(j) of the Federal Food, Drug and Cosmetic Act and complies with the requirements of Section 314.92 through 314.99 of Title 21 of the Code of Federal regulations. Ketotifen Fumarate Ophthalmic Solution, 0.025% is a sterile product which is indicated for the temporary prevention of itching of the eye due to allergic conjunctivitis.

This ANDA is being filed in CTD format and consists of eight volumes. Alcon is filing all five modules as required by the CTD format. A complete set of archive (blue folder) copies (Module 1, Module 2, Module 3, Module 4, and Module 5) is included. Review copies of Module 1, Module 2, and Module 3 are included in Chemistry, Manufacturing, and Controls (red) folders and in Microbiology (white) folders. A copy of the Bioequivalence/Bioavailability Waiver is included in the Pharmacokinetic (orange) folder.

Included in front of the first volume of the archive copy of Module 1, please find the signed copy of the 356h form, original GMP certification, original patent certification, original copies of the final printed labeling, and the original annotated labeling.

Alcon commits to the resolution of any issues identified in the methods validation process after approval.

This letter also certifies that, concurrent with the filing of the ANDA, a true copy of the technical sections of the ANDA was sent to the Dallas District Office. This "field copy" includes a copy of the FDA Form 356h and a certification that the contents are a true copy of the technical sections filed with the Office of Generic Drugs.

We appreciate the Agency's time and consideration spent in the review of this application. As appropriate, communications may be sent via facsimile to (817) 551-4630. If there are any questions, regarding the content or format of this application, do not hesitate to contact the undersigned directly at (817) 551-8568.

Sincerely,

Norma J. Schafer

Norma J. Schafer
Regulatory Affairs
Enclosures