CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020809

ADMINISTRATIVE/CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-809

Alcon Laboratories
Attention: Susan H. Caballa
Associate Director
6201 South Freeway
Fort Worth, Texas 76134

JUL 29 1997

Dear Ms. Caballa:

Please refer to your new drug application dated December 20, 1996, received December 23, 1996, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Diclofenac Sodium Ophthalmic Solution 1%.

We acknowledge receipt of your submissions dated January 6 and 17, February 5, 6, 10, and 21, March 4 and 13, April 15 and 28, and May 30, 1997.

We have completed our review and find the information presented inadequate, and the application is not approvable under section 505(d) of the Act and 21 CFR 314.125(b).

Under 21 CFR 314.125(b)(5) of the FDA implementing regulations, you have failed to provide substantial evidence consisting of adequate and well-controlled studies, as defined in 21 CFR 314.126, that Diclofenac Sodium Ophthalmic Solution 1% will have the effect it is represented to have under the conditions of use prescribed, recommended, or suggested in its proposed labeling. Specifically, the product failed to demonstrate a clinically significant change and was numerically inferior to the control product. Therefore, safety and efficacy in adequate and well-controlled trials were not established.

In addition, we have the following comments and requests for information:

[redacted]

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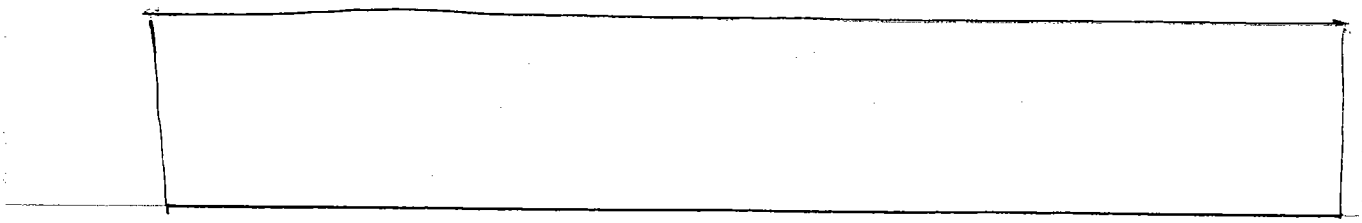


We reserve comment on the proposed labeling until the application is otherwise approvable.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of the other options under 21 CFR 314.120. In the absence of any such action FDA may proceed to withdraw the application. Any amendments should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d) of the new drug regulations, you may request an informal or telephone conference with the Division to discuss what further steps need to be taken before the application may be approved.

If you have any questions, please contact Lissante C. LoBianco, Acting Supervisory Project Manager, at (301) 827-2090.

Sincerely,

/S/ 7/14/97

Michael Weintraub, M.D.
Acting Director
Division of Anti-Inflammatory, Analgesic, and
Ophthalmic Drug Products, HFD-550
Office of Drug Evaluation V
Center for Drug Evaluation and Research

5520
Gorsh

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-809

JAN 5 1998

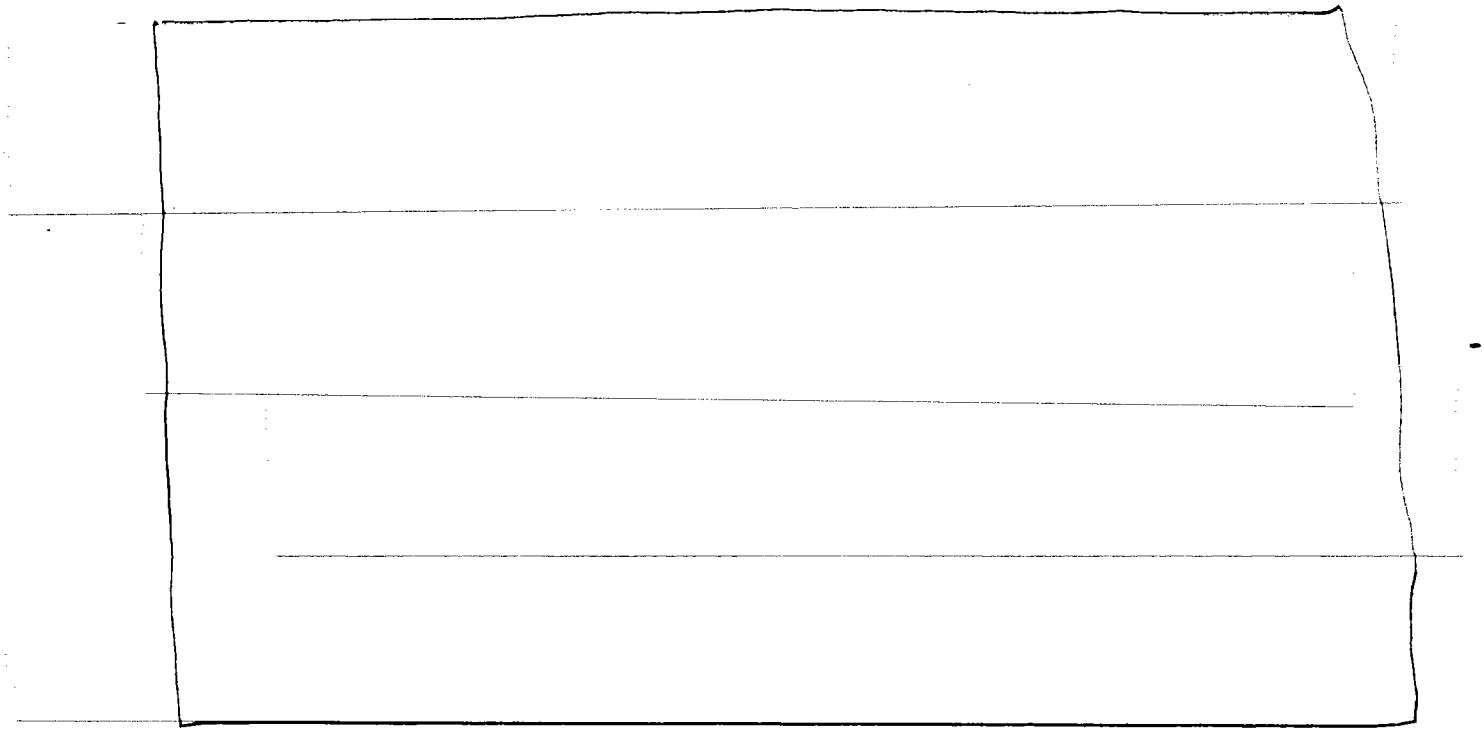
Alcon Laboratories
Attention: Susan H. Caballa
Associate Director
6201 South Freeway
Fort Worth, Texas 76134

Dear Ms. Caballa:

Please refer to your new drug application dated December 20, 1996, submitted under section 505(b)(2) of the Federal Food, Drug and Cosmetic Act for Diclofenac Sodium Ophthalmic Solution 0.1%. Reference is also made to the not approvable letter dated July 29, 1997.

We acknowledge receipt of your submissions dated August 6, 15, and 20 (2), September 10, October 24, and November 18, 1997.

We have completed the review of this application as amended and it is approvable. Before this application may be approved, however, it will be necessary for the following issues to be satisfactory resolved:



Any changes in the conditions outlined in this application and the status of the manufacturing and testing facilities' compliance with current good manufacturing procedures are subject to Agency review before final approval of the application will be made.

Please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please send one copy to the Division of Anti-Inflammatory, Analgesic and Ophthalmic Drug Products, (DAAODP), HFD-550 and two copies of both the promotional material and the package insert directly to:

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

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of the other options under 21 CFR 314.110. In the absence of such action FDA may take action to withdraw the application. Please note that under 21 CFR 314.50(d)(5)(vi)(b), an amendment to this application should include an update of safety information you now have regarding your new drug product.

Under 21 CFR 314.102 (d) of the new drug regulations you may request an informal or telephone conference with the DAAODP to discuss what further steps need to be taken before the application may be approved.

The drug may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, please contact, Ms. Lori Gorski, Project Manager, at (301) 827-2090.

Sincerely,

/S/ 1/5/98

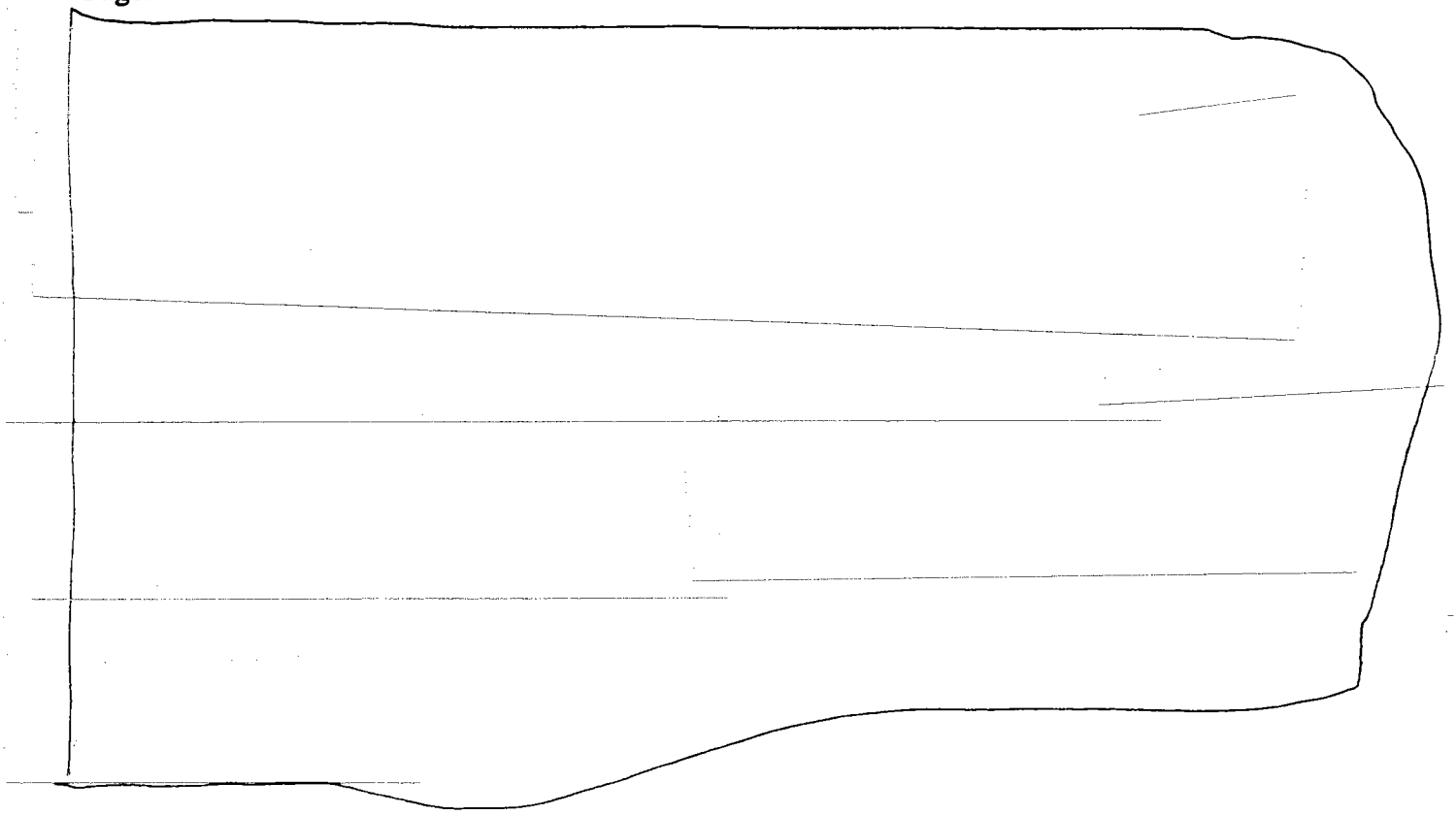
Wiley A. Chambers, M.D.
Deputy Director
Division of Anti-Inflammatory, Analgesic and
Ophthalmologic Drug Products, HFD-550
Office of Drug Evaluation V
Center for Drug Evaluation and Research

Attachment: Draft Labeling

APPEARS THIS WAY
ON ORIGINAL

THIS SECTION WAS DETERMINED **NOT** TO BE RELEASABLE

3 pages



cc: NDA 20-809
HFD-105/Weintraub
HFD-105/Walling
HFD-550/Div. Files
HFD-002/ORM
HFD-92/DDM-DIAB
HFD-830/Chem/Yaciw
HFD-550/PharmTL/Chen
HFD-725/Stat/Patrician
HFD-805/MicroTL/Cooney
HFD-880/Biopharm/Bashaw
HFD-550/PM/Gorski
HFD-550/Clin Rev/Holmes
HFD-550/MO/Chambers

Drafted by: Chambers 12/31/97
Revised by: Chambers/Yaciw/Gorski/Holmes 1/5/98

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-809

MAR 23 1998

Alcon Laboratories
Attention: Susan H. Caballa
Associate Director, Regulatory Affairs
6201 South Freeway
Fort Worth, Texas 76134

Dear Ms. Caballa:

Please refer to your new drug application (NDA) dated December 20, 1996, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Diclofenac Sodium Ophthalmic Solution, 0.1%. Reference is also made to our not approvable letter dated July 29, 1997, and approvable letter dated January 5, 1998.

We acknowledge receipt of your submissions dated January 6 and 30, February 11, 24, and 27, and March 3, 4, 6, and 13, 1998.

This new drug application provides for Diclofenac Sodium Ophthalmic Solution, 0.1% for the treatment of postoperative inflammation in patients who have undergone cataract extraction.

We have completed the review of this application and have concluded that based upon the information you have presented to date, the drug product is safe and effective for use as recommended in the submitted draft labeling dated January 30, 1998, with the revisions identified in the submission dated March 13, 1998. Accordingly, the application is **tentatively approved**. This determination is contingent upon the current information in your application and the status of current good manufacturing practices of the facilities used in the manufacturing and testing of the drug product, and is therefore subject to change on the basis of new information that may come to our attention. Any significant change in the conditions outlined in this new drug application will require Agency review before final approval may be granted.

The listed drug product referenced in your application is subject to a period of patent protection which will expire on October 2, 2007 (patent 4,960,799). You have informed us that litigation is underway in United States District Court in conjunction with Ciba Vision Corporation's patent infringement suit against Alcon. Final approval of your application cannot be granted until

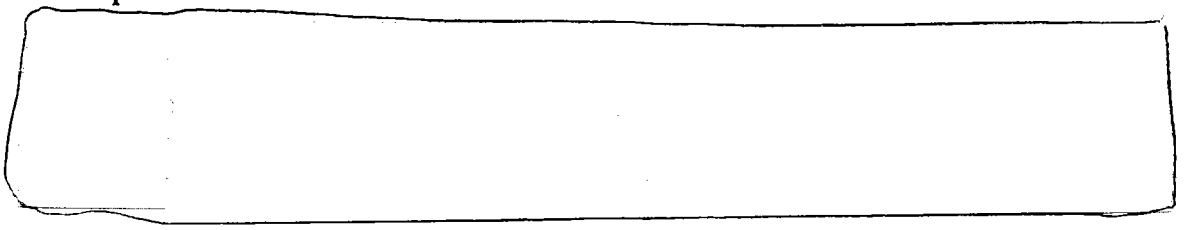
1. a. The expiration of the 30-month period (August 12, 1999) provided in section 505(c)(3)(C) since an action has been brought for infringement of a patent before the expiration of the forty-five days from the date of the notice, or

b. The date of court decision finding the patent invalid or not infringed, which has been interpreted by the Agency to mean the date of the final order or judgement of that court from which no appeal can be or has been taken, or

c. The relevant patent(s) has expired, and

2. the Agency is assured that there is no new information that would affect whether final approval should be granted.

Because the agency is granting tentative approval for this application, when you believe that your application may be considered for final approval or if you believe that there are grounds for issuing a final approval letter prior to August 12, 1999, you must amend your application to notify the Agency of the circumstances that may affect the effective date of final approval. Your amendment must provide:

1. 

2. A safety update as described in 21 CFR 314.50(d)(5)(vi)*(b)*, and

3. a. Updated final printed labeling or chemistry, manufacturing and controls data, as appropriate, and any other change in the conditions outlined in this application, or

b. A statement that no such changes have been made to the application since the date of tentative approval.

This submission should be designated as a major amendment in your cover letter. In addition to or instead of the amendment requested above, the Agency may, at any time prior to the final date of approval, request that you submit an amendment containing the information described above. Failure to submit any such amendment requested by the Agency will prompt a review of the application that may result in rescission of the tentative approval letter, or a delay in the issuance of the final approval letter.

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

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

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

Prior to the issuance of a final approval letter by the Agency your product is not deemed to be approved and will not be included in the "Approved Drug Products with Therapeutic Equivalence Evaluations" list published by the Agency.

The introduction or delivery for introduction into interstate commerce of this drug product before the effective approval date is prohibited under section 301(d) of the Act (21 U.S.C. 331(d)).

If you have any questions, please contact Lori Gorski, Project Manager, at (301) 827-2090.

Sincerely,

/S/ 3/23/98

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

ALCON LABORATORIES, INC.

PARAGRAPH IV CERTIFICATION

Pursuant to section 505(b)(2)(A) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(b)(2)(A)) ("the Act"), I, Alcon Laboratories, Inc. ("Alcon"), certify that United States Patent No. 4,960,799 ("the '799 patent") will not be infringed by the manufacture, use or sale of the Alcon Diclofenac Sodium Ophthalmic Solution 0.1% for which this application is submitted. Alcon will provide notice of the submission of this application and a detailed statement of the factual and legal basis for Alcon's opinion that the '799 patent will not be infringed, to Ciba-Geigy Corporation, 444 Saw Mill River Road, Ardsley, New York, 10502, the owner of record of the '799 patent and the holder of an approved application under section 505(b) of the Act.

Date: January 6, 1998

Patrick M. Ryan

Alcon Laboratories, Inc.
Patrick M. Ryan
Assistant General Counsel

EXCLUSIVITY SUMMARY for NDA # 20-809 **SUPPL #** —

Trade Name Diclofenac Sodium Ophthalmic Solution 0.1% **Generic Name** diclofenac Sodium ophthalmic Solution

Applicant Name Alcon Laboratories **HFD-** 550

Approval Date, if known _____

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

   a) Is it an original NDA?

   YES /✓/ NO /___/

   b) Is it an effectiveness supplement?

   YES /___/ NO /✓/

   If yes, what type? (SE1, SE2, etc.) —

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

   YES /___/ NO /✓/

   If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

   505(b)(2) application - clinical info to demonstrate equivalence to NDA 20-037

   If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES /___/ NO /___/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

_____

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use? (Rx-to-OTC switches should be answered NO-please indicate as such.)

YES /✓/ NO /___/

If yes, NDA # 20-037 Drug Name Valtrex

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /___/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /___/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /___/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

_____

_____

YES /___/ NO /___/

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

_____

_____

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

_____ _____

_____ _____

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

_____ _____

_____ _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

_____ _____

_____ _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # _____ YES /___/ NO /___/ Explain: _____

_____

Investigation #2

IND # _____ YES /___/ NO /___/ Explain: _____

_____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

Investigation #2

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

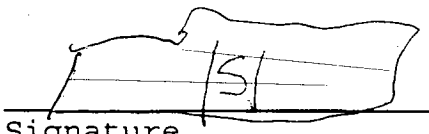
_____ _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

_____



Signature
Title: Deputy Div Director

3/25/98
Date

_____
Signature of Division Director

_____
Date

cc: Original NDA Division File HFD-93 Mary Ann Holovac

3/4/97

PATENT DECLARATION

The undersigned declares that Patent No. 5,603,929 covers the formulation, composition, and/or method of use of Diclofenac Sodium Ophthalmic Solution 0.1%. This product is the subject of this application for which approval is being sought.

Date: March 3, 1997

Alcon Laboratories, Inc.
James A. Arno
Vice President, Legal Counsel

APPEARS THIS WAY
ON ORIGINAL

US005603929A

United States Patent [19]

Desai et al.

[11] **Patent Number: 5,603,929**

[45] **Date of Patent: Feb. 18, 1997**

[54] **PRESERVED OPHTHALMIC DRUG COMPOSITIONS CONTAINING POLYMERIC QUATERNARY AMMONIUM COMPOUNDS**

[75] Inventors: **Suketu D. Desai; Diane S. Nelms**, both of Fort Worth, Tex.

[73] Assignee: **Alcon Laboratories, Inc.**, Fort Worth, Tex.

[21] Appl. No.: **340,763**

[22] Filed: **Nov. 16, 1994**

[51] **Int. Cl.**[6] **A61K 6/00**; A61K 31/74; A61K 47/00

[52] **U.S. Cl.** **424/78.04**; 424/401; 514/912; 514/913; 514/914; 514/954

[58] **Field of Search** 424/401, 78.04, 424/657, 658, 659, 660; 514/912, 913, 914, 954

[56] **References Cited**

U.S. PATENT DOCUMENTS

3,931,319	1/1976	Green et al.	260/567.6
4,027,020	5/1977	Green et al.	424/248.56
4,136,173	1/1979	Pramoda et al.	424/177
4,136,177	1/1979	Lin et al.	424/211
4,136,178	1/1979	Lin et al.	424/211
4,407,791	10/1983	Stark	424/80
4,525,346	6/1985	Stark	424/80
4,822,819	4/1989	DeSantis et al.	514/530
4,822,820	4/1989	DeSantis et al.	514/530
4,836,986	6/1989	Ogunbiyi et al.	422/28
4,861,760	8/1989	Mazuel et al.	514/54
4,960,799	10/1990	Nagy	514/567
5,037,647	8/1991	Chowhan et al.	424/78
5,110,493	5/1992	Cherng-Chyi et al.	514/413
5,149,693	9/1992	Cagle et al.	514/40
5,149,694	9/1992	Cagle et al.	514/40
5,173,507	12/1992	DeSantis et al.	514/530
5,188,826	2/1993	Chandrasekaran et al.	424/78.04
5,300,287	4/1994	Park	424/78.04
5,342,620	8/1994	Chowhan	424/422

FOREIGN PATENT DOCUMENTS

89/06964	8/1989	WIPO .
91/09523	7/1991	WIPO .
94/15597	7/1994	WIPO .

Primary Examiner—Thurman K. Page
Assistant Examiner—Sharon Howard
Attorney, Agent, or Firm—Patrick M. Ryan

[57] **ABSTRACT**

Disclosed are storage-stable preserved ophthalmic compositions containing acidic drugs in combination with polymeric quaternary ammonium compounds and boric acid.

20 Claims, No Drawings

PRESERVED OPHTHALMIC DRUG COMPOSITIONS CONTAINING POLYMERIC QUATERNARY AMMONIUM COMPOUNDS

BACKGROUND OF THE INVENTION

The present invention relates generally to ophthalmic compositions. In particular, the present invention relates to the use of a polymeric quaternary ammonium compound and boric acid to provide preserved, storage-stable ophthalmic compositions of acidic drugs.

Ophthalmic formulations generally contain one or more active compounds along with excipients such as surfactants, comforting agents, complexing agents, stabilizers, buffering systems, chelating agents, viscosity agents or gelling polymers and anti-oxidants. Ophthalmic formulations which are intended for multidose use require a preservative.

Organo-mercurials have been used as preservatives in ophthalmic formulations including ophthalmic solutions of acidic drugs. These organo-mercurials include thimerosal, phenylmercuric acetate and phenylmercuric nitrate. Organo-mercurials, however, have limitations due to potential mercury toxicity and poor chemical stability.

Sorbic acid, has also been used to preserve ophthalmic formulations, but it too possesses poor chemical stability as well as poor antimicrobial activity.

Benzalkonium chloride is a widely used preservative in ophthalmic solutions. However, benzalkonium chloride and other quaternary ammonium compounds are generally considered to be incompatible with ophthalmic compositions of drugs with acidic groups, such as nonsteroidal antiinflammatory drugs ("NSAIDS"). These preservative lose their ability to function as they form complexes with the charged drug compounds.

U.S. Pat. No. 5,110,493 discloses stable ophthalmic NSAID formulations which do not contain organo-mercurial preservatives. Instead, the reference NSAID formulations use quaternary ammonium compounds, such as cetyltrimethylammonium bromide, cetylpyridinium chloride and preferably, benzalkonium chloride, and a stabilizing amount of a nonionic surfactant.

PCT application WO 94/15597 discloses the use of lauralkonium chloride, the C_{12} homolog of benzalkonium chloride, in ophthalmic formulations of drugs which are incompatible with benzalkonium chloride. Unlike the mixture of alkyldimethylbenzylammonium chloride known as benzalkonium chloride, this PCT application discloses that lauralkonium chloride is compatible with acidic drug entities; apparently it does not form insoluble ion complexes with the charged drug compounds.

In some cases, the present lack of a single preservative which is safe, stable, and able to meet both the United States Pharmacopoeia (USP) and European Pharmacopoeia (Ph. Eur.) preservative effectiveness requirements for ophthalmic formulations of acidic drugs has forced pharmaceutical companies to develop more than one formulation of the same drug, with each formulation containing a different preservative.

U.S. Pat. No. 4,960,799 discloses storage stable aqueous ophthalmic compositions containing diclofenac, a nonsteroidal antiinflammatory drug, and/or its pharmaceutically acceptable salts. The reference compositions include EDTA as a stabilizing agent, a solubilizer such as polyethoxylated castor oil, and a bacteriostat. The preferred bacteriostats are thimerosal and sorbic acid. No mention is made of any polymeric quaternary ammonium preservative.

The use of POLYQUAD® and other polymeric quaternary ammonium compounds as a disinfectant and preservative in contact lens care and artificial tear solutions is known. See, for example, U.S. Pat. Nos. 5,037,647; 4,525,346; and 4,407,791.

U.S. Pat. No. 4,525,346, in addition to disclosing applications in contact lens and artificial tear solutions, also discloses the use of certain polymeric quaternary ammonium compounds in formulations containing certain ophthalmic drugs. However, neither this reference nor any of the other references mentioned above discloses the use of a polymeric quaternary ammonium compound as a preservative in formulations of acidic ophthalmic drugs, that is, drugs which may be incompatible with positively charged preservatives.

SUMMARY OF THE INVENTION

It has now been discovered that the use of a combination of a polymeric quaternary ammonium compound such as POLYQUAD® and boric acid in ophthalmic compositions of acidic drugs provides a storage-stable composition which has surprisingly good preservative efficacy. This preservative combination of a polymeric quaternary ammonium compound and boric acid is useful in ophthalmic compositions of acidic drugs such as prostaglandins, antifungals, antibactedals, and diagnostic agents. This preservative combination is especially useful in ophthalmic solutions of drugs containing either a carboxyl group such as non-steroidal anti-inflammatory drugs (NSAIDS) or a sulfonamide group such as antibacterial drugs.

The present invention also relates to a method for treating or controlling ocular inflammation which comprises topically administering to the affected eye a composition comprising a NSAID, a polymeric quaternary ammonium compound and boric acid.

Among other factors, the present invention is based on the discovery that ophthalmic compositions containing a polymeric quaternary ammonium compound and boric acid may be effectively preserved by the USP and Ph. Eur. preservative effectiveness requirements despite the absence of EDTA, a conventional chelating agent known to potentiate the antimicrobial activity of preservatives such as benzalkonium chloride and sorbic acid.

DETAILED DESCRIPTION OF THE INVENTION

The polymeric quaternary ammonium compounds useful in the compositions of the present invention are those which have an antimicrobial effect and which are ophthalmically acceptable. Preferred compounds of this type are described in U.S. Pat. Nos. 3,931,319; 4,027,020; 4,407,791; 4,525,346; 4,836,986; 5,037,647 and 5,300,287; and PCT application WO 91/09523 (Dziabo et al.). The most preferred polymeric ammonium compound is polyquaternium 1, otherwise known as POLYQUAD® or ONAMERM® with a number average molecular weight between 2,000 to 30,000. Preferably, the number average molecular weight is between 3,000 to 14,000.

The polymeric quaternary ammonium compounds are generally used in the compositions of the present invention in an amount from about 0.00001 to about 3 wt %, preferably from about 0.001 to about 0.1 wt %. Most preferably, the compositions of the present invention contain from about 0.001 to about 0.05 wt % of polymeric quaternary ammonium compounds.

The boric acid used in the compositions of the present invention includes not only boric acid, but also its ophthalmically acceptable acid addition salts, as well as borate-polyol complexes of the type described in U.S. Pat. No. 5,342,620 (Chowhan). In general, an amount from about 0.3 to about 5.0 wt % is used in the compositions of the present invention. It is preferred to use from about 0.3 to about 3.0 wt %, and it most preferred to use from about 0.5 to about 2.0 wt %. The water soluble borate-polyol complexes useful in the compositions of the present invention preferably comprise borate and polyol in a molar ratio between about 1:1 and about 1:10.

Suitable ophthalmic agents which may be included in the compositions of the present invention and administered via the method of the present invention include, but are not limited to, the racemic and enantiomeric forms and ophthalmically acceptable salts, amides, esters and prodrugs of the following types of drugs containing an acidic functionality such as —COOH, —SO_2NH_2, or SO_2NHR groups: anti-glaucoma agents, such as carbonic anhydrase inhibitors, prostaglandins and prostaglandin derivatives; non-steroidal anti-inflammatory agents, including but not limited to those classified as aryl- or heteroaryl- alkanoic acids, such as diclofenac, bromfenac, flurbiprofen, suprofen, ketorolac, indomethacin and ketoprofen; anti-bacterials and anti-infectives, including sulfa drugs, such as sulfacetamide sodium, and beta-lactams such as penicillins and cephalosporins; and diagnostic agents such as sodium fluorescein. Combinations of ophthalmic agents may also be used in the compositions of the present invention.

The compositions of the present invention may additionally include other ophthalmically acceptable components such as comfort enhancing agents, buffers (e.g., phosphate, acetate, carbonate, and citrate), other preservatives (e.g., benzalkonium chloride and individual homologs of benzalkonium chloride, parabens, chlorobutanol, and biguanides such as chlorhexidine and hydroxypropyl methyl biguanide), surfactants (e.g. poloxamers such as Pluronics®; polysorbates such as Tweens®; tyloxapol; sarcosinates such as Hamposyl®; and polyethoxylated castor oils such as Cremophor®), and tonicity agents (e.g., sodium chloride, mannitol, dextrose and xylitol). In addition, other excipients, such as antioxidants, chelating agents and complexing agents may be added to the compositions of the present invention as desired or as necessary.

The compositions of the present invention may also include viscosity modifying agents such as: cellulosic ethers, such as, hydroxypropyl methyl cellulose (HPMC), hydroxyethyl cellulose (HEC), ethyl hydroxyethyl cellulose, hydroxypropyl cellulose, methyl cellulose, and carboxymethyl cellulose; carbomers (e.g. Carbopol®); polyvinyl alcohol; polyvinyl pyrrolidone; alginates; carrageenans; and guar, karaya, agarose, locust bean, tragacanth and xanthan gums. The concentration of such viscosity modifiers will vary between about 0.1 to about 5 wt %, but such formulations will generally have a viscosity between about 10 and about 5000 centipoise.

The ophthalmic compositions of the present invention may additionally contain polymers which will undergo sol-to-gel transition upon exposure to physical or chemical stimuli, such as changes in pH, ion concentration, and/or temperature. Examples of such polymers include but are not limited to: certain carrageenans, and gellan, locust and xanthan gums, such as those described in U.S. Ser. No. 08/108,824 (Lang et al.), U.S. Pat. No. 4,861,760 (Mazuel et al), U.S. Pat. No. 4,136,173 (Pramoda et al), U.S. Pat. No. 4,136,177 (Linet al.), and U.S. Pat. No. 4,136,178 (Linet al). The contents of these patent applications and patents relating to the polymers cited above are hereby incorporated by reference herein.

The acidic drugs in the compositions of the present invention may also be encapsulated in microparticles such as microcapsules, microspheres, nanocapsule, nanospheres, and liposomes to improve comfort, and/or provide for sustained release. The following examples are presented to illustrate further various aspects of the present invention, but are not intended to limit the scope of the invention in any respect.

EXAMPLE 1

The following formulations are representative of preferred compositions of the present invention.

	Formulation (wt %)		
Ingredient	A	B	C
Sodium Diclofenac	0.1	—	—
Sulfacetamide	—	10	—
Sodium Suprofen	—	—	0.25
HPMC*	0.1	0.1	0.1
Tromethamine	2.0	2.0	2.0
Boric Acid	1.2	1.2	1.2
Vitamin E TPGS**	3.0	3.0	3.0
Mannitol	3.5	1.6	3.6
POLYQUAD ®	4	0.005	0.005
HCl/NaOH	q.s. to pH 7.4	q.s. to pH 7.4	q.s. to pH 7.4
Purified Water	q.s. to 100%	q.s. to 100%	q.s. to 100%

*Hydroxypropyl Methyl Cellulose
**Vitamin E Tocopheryl Polyethylene Glycol 1000 Succinate

Preparation

The preparation of Formulation A is detailed below. Formulations B and C can be prepared in similar fashion.

Initially, a 10% stock solution of TPGS and a 2% stock solution of HPMC were prepared in water under constant stirring. Heat was applied if necessary to ensure complete dissolution.

To a tared glass vessel containing approximately 40% final weight of purified water was added diclofenac-sodium. This mixture was stirred until the diclofenac was completely dissolved. The following ingredients were then added with stirring in the order given below, and each ingredient was completely dissolved before addition of the next ingredient: stock solution of vitamin E TPGS; tromethamine; boric acid; Polyquad®; mannitol; and stock solution of HPMC.

Water was then added to bring the formulation to 95% of its final weight, and the pH of the formulation adjusted to between 7 and 7.4 using NaOH and/or HCl. Water was then added to bring the final weight to 100%. The resulting formulations were approximately isotonic (above 300 milliOsmoles per kilogram (mOsm/kg)).

EXAMPLE 2

The antimicrobial preservative effectiveness of the polymeric quaternary ammonium compound/boric acid combination of the present invention was determined using an organism challenge test according to the methods described in the United States Pharmacopeia XXII (USP) and European Pharmacopoeia (1994(Ph. Eur.). Samples were inoculated with known levels of gram-positive (*Staphylococcus aureus* ATCC 6538) and gram-negative (*Pseudomonas aeruginosa* ATCC 9027 and *Escherichia coil* ATCC 8739)

vegetative bacteria, yeast (*Candida albicans* ATCC 10231) and mold (*Aspergillus niger* ATCC 16404) and sampled at specified intervals to determine if the antimicrobial preservative system was capable of killing or inhibiting the propagation of organisms purposely introduced into the formulation. The rate or level of antimicrobial activity determined compliance with the USP and/or Ph. Eur. preservative efficacy standards for ophthalmic preparations.

The compendial preservative standards for ophthalmic preparations are presented below:

	Log Reduction of Organism Population		
Time Pull	USP	*Ph. Eur.* A (Target)	*Ph. Eur.* B (Min)
	For Bacteria:		
6 hours	—	2	—
24 hours	—	3	1
7 days	—	—	3
14 days	3	—	—
28 days	NI	NR	NI
	For Fungi:		
7 days	—	2	—
14 days	NI	—	1
28 days	NI	NI	NI

NR = No organisms recovered
NI = No increase at this or any following time pulls
— = No requirement at this time pull

The results of the preservative challenge study conducted on Formulation A are shown below in Table 1. These results illustrate that an ophthalmic formulation of an acidic drug can be globally preserved, that is, can comply with the USP and Ph. Eur. A preservative effectiveness requirements for ophthalmic preparations, using a combination of a polymeric quaternary ammonium compound and boric acid.

TABLE 1

	Preservative Challenge Results for Formulation A						
TEST	INITIAL	Number of Microorganisms Per Milliliter*					
ORGANISM	COUNT	6 Hr	24 Hr	Day 7	Day 14	Day 21	Day 28
S. aureus	1.5×10^6	<10	<10	<10	<10	<10	<10
P. aeruginosa	1.0×10^6	<10	<10	<10	<10	<10	<10
E. coli	1.1×10^6	<10	<10	<10	<0	<10	<10
C. albicans	1.2×10^6	6.3×10^5	4.1×10^4	4.4×10^2	<10	<10	<10
A. niger	1.3×10^6	1.4×10^6	3.9×10^4	2.5×10^2	8.0×10^1	6.5×10^1	<10

*Limit of detection: <10 CFU/mL

The invention has been described by reference to certain preferred embodiments; however, it should be understood that it may be embodied in other specific forms or variations thereof without departing from its spirit or essential characteristics. The embodiments described above are therefore considered to be illustrative in all respects and not restrictive, the scope of the invention being indicated by the appended claims rather than by the foregoing description.

What is claimed is:

1. A storage stable ophthalmic composition comprising a therapeutically effective amount of one or more acidic ophthalmic agents, a combination of an antimicrobial polymeric quaternary ammonium compound and boric acid in an amount effective to meet at least the minimum United States Pharmacopeia XXII and European Pharmacopeia (1994) preservative effectiveness requirements, and an ophthalmically acceptable vehicle; wherein the acidic ophthalmic agent is selected from the group consisting of anti-glaucoma and non-steroidal anti-inflammatory agents; provided that the composition does not contain a viscosity-enhancing amount of polyvinyl alcohol.

2. The composition of claim **1** wherein the ophthalmic agent is a non-steroidal anti-inflammatory agent.

3. The composition of claim **2** wherein the non-steroidal anti-inflammatory agent comprises an aryl- or heteroarylalkanoic acid, or an ophthalmically acceptable salt, ester, amide, or prodrug thereof.

4. The composition of claim **3** wherein the non-steroidal anti-inflammatory agent is selected from the group consisting of: diclofenac, flurbiprofen, suprofen, bromfenac, ketorolac, indomethacin, ketaprofen, and ophthalmically acceptable salts, esters, amides or prodrugs thereof.

5. The composition of claim **4** wherein the non-steroidal anti-inflammatory agent is selected from the group consisting of diclofenac and its ophthalmically acceptable salts, esters, amides, or prodrugs thereof.

6. The composition of claim **4** wherein the non-steroidal anti-inflammatory agent is selected from the group consisting of suprofen and its ophthalmically acceptable salts, esters, amides, or prodrugs thereof.

7. The composition of claim **4** wherein the non-steroidal anti-inflammatory agent is selected from the group consisting of bromfenac and its ophthalmically acceptable salts, esters, amides, or prodrugs thereof.

8. The composition of claim **7** wherein the antimicrobial polymeric quaternary ammonium compound is polyquaternium 1.

9. The composition of claim **8** wherein the polyquaternium 1 has a number average molecular weight from 2,000 to 30,000.

10. The composition of claim **9** wherein the polyquaternium 1 has a number average molecular weight from 3,000 to 14,000.

11. The composition of claim **1** wherein the concentration of the antimicrobial polymeric quaternary ammonium compound is between about 0.00001 and about 3 percent by weight.

12. The composition of claim **11** wherein the concentration of the antimicrobial polymeric quaternary ammonium compound is between about 0.001 and about 0.1 percent by weight.

13. The composition of claim **12** wherein the concentration of the antimicrobial polymeric quaternary ammonium compound is between about 0.001 and about 0.05 percent by weight.

14. The composition of claim **1** wherein the ophthalmically active forms of boric acid are selected from the group

consisting of boric acid, ophthalmically acceptable acid addition salts of boric acid and borate-polyol complexes.

15. The composition of claim 1 wherein the concentration of boric acid is between about 0.3 and about 5.0 percent by weight.

16. The composition of claim **15** wherein the concentration of boric acid or ophthalmically active forms thereof is between about 0.3 and about 3 percent by weight.

17. The composition of claim **16** wherein the concentration of boric acid or ophthalmically active forms thereof is between about 0.5 and about 2 percent by weight.

18. The composition of claim 14 wherein the ophthalmically active forms of boric acid are water soluble borate-polyol complexes having a molar ratio of borate to polyol from 1:1 to 1:10.

19. An ophthalmic formulation comprising diclofenac or an ophthalmically acceptable salt, ester, amide or prodrug thereof, and a combination of an antimicrobial polymeric quaternary ammonium compound and boric acid in an amount effective to meet at least the minimum United States Pharmacopeia XXII and European Pharmacopeia (1994) preservative effectiveness requirements; provided, that the formulation does not contain a viscosity-enhancing amount of polyvinyl alcohol.

20. The formulation of claim **19** wherein the formulation comprises sodium diclofenac, boric acid, mannitol, polyquaternium 1 and a comfort-enhancing agent.

* * * * *

DUPLICATE

Certified Mail Z 047 939 726
Return Receipt Requested

Alcon LABORATORIES

ALCON LABORATORIES, INC.
6201 SOUTH FREEWAY
FORT WORTH, TEXAS 76134-2099
(817) 293-0450

August 15, 1997

Division of Analgesic, Anti-Inflammatory and
Ophthalmic Drug Products, HFD-550
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard
Rockville, Maryland 20850

Re: NDA 20-809
Diclofenac Sodium Ophthalmic Solution 0.1%
Amendment to a Pending Application

Dear Sir/Madam:

Pursuant to the provisions of 21 CFR § 314.53(c)(2)(i) and (ii), Alcon is amending its application to provide additional patent information. Patent 5,653,972 was assigned to Alcon Laboratories on August 5, 1997 with an expiration date of November 16, 2014. An original declaration and a copy of Patent 5,653,972 are appended.

I may be reached at (817) 568-6296 should you require additional information.

Sincerely,

Susan H. Caballa
Assoc. Director
Regulatory Affairs

312..fda

US005653972A

United States Patent [19]

Desai et al.

[11] Patent Number: 5,653,972

[45] Date of Patent: Aug. 5, 1997

[54] **PRESERVED OPHTHALMIC DRUG COMPOSITIONS CONTAINING POLYMERIC QUATERNARY AMMONIUM COMPOUNDS**

[75] Inventors: **Suketu Dipakbhai Desai; Diane S. Nelms**, both of Fort Worth, Tex.

[73] Assignee: **Alcon Laboratories, Inc.**, Fort Worth, Tex.

[21] Appl. No.: **700,960**

[22] Filed: **Aug. 21, 1996**

Related U.S. Application Data

[62] Division of Ser. No. 340,763, Nov. 16, 1994.

[51] **Int. Cl.**[6] **A61K 9/08**; A61K 31/74

[52] **U.S. Cl.** **424/78.04**; 424/405; 424/422; 424/427; 514/772.3; 514/912; 514/954

[58] **Field of Search** 424/405, 78.04, 424/422, 427; 514/772.3, 912, 954

[56] **References Cited**

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Primary Examiner—Thurman K. Page
Assistant Examiner—Sharon Howard
Attorney, Agent, or Firm—Patrick M. Ryan

[57] **ABSTRACT**

Disclosed are storage-stable preserved ophthalmic compositions containing acidic drugs in combination with polymeric quaternary ammonium compounds and boric acid.

5 Claims, No Drawings

APPEARS THIS WAY
ON ORIGINAL

invention. It is preferred to use from about 0.3 to about 3.0 wt %, and it most preferred to use from about 0.5 to about 2.0 wt %. The water soluble borate-polyol complexes useful in the compositions of the present invention preferably comprise borate and polyol in a molar ratio between about 1:1 and about 1:10.

Suitable ophthalmic agents which may be included in the compositions of the present invention and administered via the method of the present invention include, but are not limited to, the racemic and enantiomeric forms and ophthalmically acceptable salts, amides, esters and prodrugs of the following types of drugs containing an acidic functionality such as —COOH, $—SO_2NH_2$, or SO_2NHR groups: anti-glaucoma agents, such as carbonic anhydrase inhibitors, prostaglandins and prostaglandin derivatives; non-steroidal anti-inflammatory agents, including but not limited to those classified as aryl- or heteroaryl- alkanoic acids, such as diclofenac, bromfenac, flurbiprofen, suprofen, ketorolac, indomethacin and ketoprofen; anti-bacterials and anti-infectives, including sulfa drugs, such as sulfacetamide sodium, and beta-lactams such as penicillins and cephalosporins; and diagnostic agents such as sodium fluorescein. Combinations of ophthalmic agents may also be used in the compositions of the present invention.

The compositions of the present invention may additionally include other ophthalmically acceptable components such as comfort enhancing agents, buffers (e.g., phosphate, acetate, carbonate, and citrate), other preservatives (e.g., benzalkonium chloride and individual homologs of benzalkonium chloride, parabens, chlorobutanol, and biguanides such as chlorhexidine and hydroxypropyl methyl biguanide), surfactants (e.g. poloxamers such as Pluronics®; polysorbates such as Tweens®; tyloxapol; sarcosinates such as Hamposyl®; and polyethoxylated castor oils such as Cremophor®), and tonicity agents (e.g., sodium chloride, mannitol, dextrose and xylitol). In addition, other excipients, such as antioxidants, chelating agents and complexing agents may be added to the compositions of the present invention as desired or as necessary.

The compositions of the present invention may also include viscosity modifying agents such as: cellulosic ethers, such as, hydroxypropyl methyl cellulose (HPMC), hydroxyethyl cellulose (HEC), ethyl hydroxyethyl cellulose, hydroxypropyl cellulose, methyl cellulose, and carboxymethyl cellulose; carbomers (e.g. Carbopol®); polyvinyl alcohol; polyvinyl pyrrolidone; alginates; carrageenans; and guar, karaya, agarose, locust bean, tragacanth and xanthan gums. The concentration of such viscosity modifiers will vary between about 0.1 to about 5 wt %, but such formulations will generally have a viscosity between about 10 and about 5000 centipoise.

The ophthalmic compositions of the present invention may additionally contain polymers which will undergo sol-to-gel transition upon exposure to physical or chemical stimuli, such as changes in pH, ion concentration, and/or temperature. Examples of such polymers include but are not limited to: certain carrageenans, and gellan, locust and xanthan gums, such as those described in U.S. Ser. No. 08/108.824 (Lang et al.), U.S. Pat. No. 4.861.760 (Mazuel et al), U.S. Pat. No. 4.136.173 (Pramoda et al), U.S. Pat. No. 4.136.177 (Lin et al.), and U.S. Pat. No. 4.136.178 (Lin et al). The contents of these patent applications and patents relating to the polymers cited above are hereby incorporated by reference herein.

The acidic drugs in the compositions of the present invention may also be encapsulated in microparticles such as microcapsules, microspheres, nanocapsule, nanospheres, and liposomes to improve comfort, and/or provide for sustained release.

The following examples are presented to illustrate further various aspects of the present invention, but are not intended to limit the scope of the invention in any respect.

EXAMPLE 1

The following formulations are representative of preferred compositions of the present invention.

	Formulation (wt %)		
Ingredient	A	B	C
Sodium Diclofenac	0.1	—	—
Sulfacetamide Sodium	—	10	—
Suprofen	—	—	0.25
HPMC*	0.1	0.1	0.1
Tromethamine	2.0	2.0	2.0
Boric Acid	1.2	1.2	1.2
Vitamin E TPGS**	3.0	3.0	3.0
Mannitol	3.5	1.6	3.6
Polyquad ®	0.005	0.005	0.005
HCl/NaOH	q.s. to pH 7.4	q.s. to pH 7.4	q.s. to pH 7.4
Purified Water	q.s. to 100%	q.s. to 100%	q.s. to 100%

*Hydroxypropyl Methyl Cellulose
**Vitamin E Tocopheryl Polyethylene Glycol 1000 Succinate

Preparation

The preparation of Formulation A is detailed below. Formulations B and C can be prepared in similar fashion.

Initially, a 10% stock solution of TPGS and a 2% stock solution of HPMC were prepared in water under constant stirring. Heat was applied if necessary to ensure complete dissolution.

To a tared glass vessel containing approximately 40% final weight of purified water was added diclofenac-sodium. This mixture was stirred until the diclofenac was completely dissolved. The following ingredients were then added with stirring in the order given below, and each ingredient was completely dissolved before addition of the next ingredient: stock solution of vitamin E TPGS; tromethamine; boric acid; Polyquad®; mannitol; and stock solution of HPMC.

Water was then added to bring the formulation to 95% of its final weight, and the pH of the formulation adjusted to between 7 and 7.4 using NaOH and/or HCl. Water was then added to bring the final weight to 100%. The resulting formulations were approximately isotonic (above 300 milliOsmoles per kilogram (mOsm/kg)).

EXAMPLE 2

The antimicrobial preservative effectiveness of the polymeric quaternary ammonium compound/boric acid combination of the present invention was determined using an organism challenge test according to the methods described in the United States Pharmacopeia XXII (USP) and European Pharmacopoeia (1994) (Ph.Eur.). Samples were inoculated with known levels of gram-positive (*Staphylococcus aureus* ATCC 6538) and gram-negative (*Pseudomonas aeruginosa* ATCC 9027 and *Escherichia coli* ATCC 8739) vegetative bacteria, yeast (*Candida albicans* ATCC 10231) and mold (*Aspergillus niger* ATCC 16404) and sampled at specified intervals to determine if the antimicrobial preservative system was capable of killing or inhibiting the propagation of organisms purposely introduced into the