CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-528

ADMINISTRATIVE DOCUMENTS
CORRESPONDENCE

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information		
NDA 21-528	Efficacy Supplement Type SE-	Supplement Number
Drug: **Acular LS (ketorolac tromethamine ophthalmic solution) 0.4%**	Applicant: **Allergan, Inc.**	
RPM: Raphael R. Rodriguez	HFD- 550	Phone # 827-2090
Application Type: **505 (b)**	Reference Listed Drug (NDA #, Drug name):	

❖ Application Classifications:	
• Review priority	(X) Standard ( ) Priority
• Chem class (NDAs only)	
• Other (e.g., orphan, OTC)	
❖ User Fee Goal Dates	June 7, 2003
❖ Special programs (indicate all that apply)	(X) None Subpart H ( ) 21 CFR 314.510 (accelerated approval) ( ) 21 CFR 314.520 (restricted distribution) ( ) Fast Track ( ) Rolling Review
❖ User Fee Information	
• User Fee	(X) Paid
• User Fee waiver	( ) Small business ( ) Public health ( ) Barrier-to-Innovation ( ) Other
• User Fee exception	( ) Orphan designation ( ) No-fee 505(b)(2) ( ) Other
❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	( ) Yes (X) No
• This application is on the AIP	( ) Yes (X) No
• Exception for review (Center Director's memo)	
• OC clearance for approval	
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification and certifications from foreign applicants are co-signed by U.S. agent.	(X) Verified
❖ Patent	
• Information: Verify that patent information was submitted	(X) Verified
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted	21 CFR 314.50(i)(1)(*i*)(A) ( ) I ( ) II ( ) III ( ) IV 21 CFR 314.50(i)(1) ( ) (ii) ( ) (iii)
• For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice).	( ) Verified

❖ Exclusivity Summary (approvals only)	5/30/03
Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)*	
General Information	
❖ Actions	
• Proposed action	(X) AP ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	
• Status of advertising (approvals only)	( ) Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	(X) Yes ( ) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	(X) None ( ) Press Release ( ) Talk Paper ( ) Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable)	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	[redacted]
• Most recent applicant-proposed labeling	5/20/03
• Original applicant-proposed labeling	8/6/02
• Labeling reviews (including DDMAC, Office of Drug Safety trade name review, nomenclature reviews) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	DMETS 4/25/03
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	
Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	[redacted]
• Applicant proposed	8/6/02
• Reviews	11/1/02; 5/28/03
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	N/A
• Documentation of discussions and/or agreements relating to post-marketing commitments	N/A
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	
❖ Memoranda and Telecons	
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	5/23/01
• Pre-NDA meeting (indicate date)	5/20/02
• Pre-Approval Safety Conference (indicate date; approvals only)	
• Other	
❖ Advisory Committee Meeting	
• Date of Meeting	N/A
• 48-hour alert	N/A
Federal Register Notices, DESI documents, NAS, NRC (if any are applicable)	N/A

Clinical and Summary Information	
Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)*	
❖ Clinical review(s) *(indicate date for each review)*	11/1/02; 2/19/03; 5/28/03
❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	
❖ Safety Update review(s) *(indicate date or location if incorporated in another review)*	5/28/03
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	5/29/03
❖ Statistical review(s) *(indicate date for each review)*	2/5/03
❖ Biopharmaceutical review(s) *(indicate date for each review)*	3/21/03
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	N/A
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	2/5/03
• Bioequivalence studies	N/A
CMC Information	
❖ CMC review(s) *(indicate date for each review)*	4/17/03
❖ Environmental Assessment	
• Categorical Exclusion *(indicate review date)*	
• Review & FONSI *(indicate date of review)*	N/A
• Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Micro (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	3/7/03
Facilities inspection (provide EER report)	Date completed: 5/20/03 (X) Acceptable ( ) Withhold recommendation
❖ Methods validation	( ) Completed (X) Requested ( ) Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	10/15/02
❖ Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	N/A
❖ CAC/ECAC report	N/A

Number of Pages Redacted 7

❖❖❖

Draft Labeling
(not releasable

EXCLUSIVITY SUMMARY for NDA # 21-528 SUPPL # _____

Trade Name ACULAR LS Generic Name Ketorolac Tromethamine Ophthalmic Solution 0.4%

Applicant Name Allergan, Inc. HFD- 550
Approval Date _____

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 questions about the submission.

   a) Is it an original NDA? YES/_X_/ NO /___/

   b) Is it an effectiveness supplement? YES /___/ NO /_X_/

      If yes, what type(SE1, SE2, etc.)? 3S - new formulation

   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 /_X_/ 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.

      _____

      _____

      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 /_X_/ NO /___/

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

3 years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /_X_/ NO /__/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

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 /_X_/

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

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

YES /___/ NO /_X_/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (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 /_X_/ NO /___/

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

NDA # 19-700 _____

NDA # 20-811 _____

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 /_X_/

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

NDA # N/A _____ _____

NDA # _____ _____

NDA # _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. 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 /_X_/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

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.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(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 /_X_/ 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 9:**

_____

_____

(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 /_X_/

(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 /_X_/

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:

Investigation #1, Study # 191578-002

Investigation #2, Study # 191578-003

Investigation #3, Study # _____

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 /_X_/
Investigation #2	YES /___/	NO /_X_/
Investigation #3	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:

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

(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 /_X_/

Investigation #2 YES /___/ NO /_X_/

Investigation #3 YES /___/ NO /___/

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

NDA # _____ Study # _____

NDA # _____ Study # _____

NDA # _____ Study # _____

(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"):

Investigation #1, Study # 191578-002
Investigation #2, Study # 191578-003
Investigation #__, Study # _____

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 # [redacted] YES /_X_/ NO /___/ Explain: _____

Investigation #2

IND [redacted] YES /_X_/ 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 /_X_/

If yes, explain: _____

_____

_____

Raphael R. Rodriguez, PM

Lucious Lim, Clinical Reviewer

/S/

Wiley A. Chambers, M.D.
Deputy Director, HFD-550

5/30/3

Date

cc:
Archival NDA 21-528
HFD-550 /Division File
HFD-550 /RPM/ RodriguezR
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/01

PEDIATRIC PAGE

(Complete for all APPROVED original applications and efficacy supplements)

NDA/BLA # : 21-528 Supplement Type (e.g. SE5): _____ Supplement Number: _____

Stamp Date: 8/9/02 Action Date: _____

HFD 550 Trade and generic names/dosage form: Acular LS (ketorolac tromethamine ophthalmic solution) 0.4%

Applicant: Allergan, Inc Therapeutic Class: Non-steroidal anti-inflammatory agent

Indication(s) previously approved: 1.) Temporary relief of ocular itching due to seasonal allergic conjunctivitis
2.) Treatment of postoperative inflammation in patients who have undergone cataract extraction
3.) Reduction of ocular pain and photophobia following incisional refractive surgery

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: Reduction of ocular pain and ocular symptom of burning/stinging following corneal refractive surgery.

Is there a full waiver for this indication (check one)?

XX Yes: Please proceed to Section A.

☐ No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

☐ Products in this class for this indication have been studied/labeled for pediatric population
☐ Disease/condition does not exist in children
☐ Too few children with disease to study
☐ There are safety concerns
XX Other: The indication is not applicable to the pediatric population. Corneal refractive surgery is contraindicated in children.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min_____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for partial waiver:

☐ Products in this class for this indication have been studied/labeled for pediatric population
☐ Disease/condition does not exist in children
☐ Too few children with disease to study
☐ There are safety concerns

- ☐ Adult studies ready for approval
- ☐ Formulation needed
- ☐ Other:_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for deferral:

- ☐ Products in this class for this indication have been studied/labeled for pediatric population
- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease to study
- ☐ There are safety concerns
- ☐ Adult studies ready for approval
- ☐ Formulation needed

Other:_____

Date studies are due (mm/dd/yy): _____

udies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

Lucious Lim, Clinical Reviewer

Raphael Rodriguez, PM

cc: NDA
HFD-950/ Terrie Crescenzi
HFD-960/ Grace Carmouze
(revised 9-24-02)
FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960
301-594-7337

REQUEST FOR WAIVER OF PEDIATRIC STUDIES

In accordance with CFR 314.55(c)(2)(i), Allergan, Inc., is requesting a waiver of the pediatric study requirements for this original New Drug Application for Ketorolac Tromethamine Ophthalmic Solution 0.4%. Allergan, Inc., is requesting this waiver based on the following reasons: This proposed new product is not likely to be used in a substantial number of pediatric patients based on the proposed indication of "the reduction of ocular pain and ocular symptoms of foreign body sensation, burning/stinging, tearing, and photophobia following refractive surgery". Additionally, Allergan previously submitted a Pediatric Study Report to the Agency on June 18, 2001 for NDA 19-700 and NDA 20-811 which was done with the same active ingredient, ketorolac tromethamine, formulated at 0.5% in pediatric patients between 3 and 12 years of age. This pediatric study was subsequently approved by the Agency on February 8, 2002 and pediatric exclusivity was granted to the above mentioned NDAs.

Peter Kresel
Senior Vice President
Global Regulatory Affairs

July 26, 2002
Date

**APPEARS THIS WAY
ON ORIGINAL**

CONSULTATION RESPONSE

DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(DMETS; HFD-420)

DATE RECEIVED: January 29, 2003	DUE DATE: April 23, 2003	ODS CONSULT #: 02-0195-1

TO: Lee Simon
Director, Division of Anti-Inflammatory, Analgesic and Ophthalmologic Drug Products
HFD-550

THROUGH: Raphael Rodriguez
Project Manager
HFD-550

PRODUCT NAME:	NDA SPONSOR:
Acular PRO (Ketorolac Tromethamine Ophthalmic Solution) 0.4% **NDA: 21-528**	Allergan, Inc

SAFETY EVALUATOR: Denise P. Toyer, Pharm.D.

SUMMARY: In response to a consult from the Division of Anti-Inflammatory, Analgesic and Ophthalmologic Drug Products (HFD-550), the Division of Medication Errors and Technical Support (DMETS) conducted a review of the proposed proprietary name "Acular [redacted] to determine the potential for confusion with approved proprietary and established names as well as pending names.

RECOMMENDATIONS:

1. DMETS does not recommend the use of the modifier [redacted] in conjunction with the proprietary name, Acular for this 0.4% formulation of Ketorolac Tromethamine. Additionally, DMETS does not recommend use of any modifier in conjunction with Acular Ophthalmic Solution 0.4%.

2. DMETS recommends that the sponsor provide an educational campaign to health care practitioners upon launch of the new strength.

3. DMETS also recommends implementation of the labeling revision outlined in Section III of this review.

4. DDMAC does not recommend use of the proprietary name Acular [redacted] from a promotional perspective for the following reason: [redacted] implies the drug is superior to other treatment options.

Carol Holquist, RPh
Deputy Director,
Division of Medication Errors and Technical Support
Office of Drug Safety
Phone: (301) 827-3242 Fax: (301) 443-9664

Jerry Phillips, RPh
Associate Director
Office of Drug Safety
Center for Drug Evaluation and Research
Food and Drug Administration

Division of Medication Errors and Technical Support (DMETS)
Office of Drug Safety
HFD-420; Parklawn Rm. 6-34
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: April 8, 2003

NDA # 21-528

NAME OF DRUG: Acular —
(Ketorolac Tromethamine Ophthalmic Solution) 0.4%

NDA HOLDER: Allergan, Inc.

I. INTRODUCTION:

This consult was written in response to a request from the Division of Anti-Inflammatory, Analgesic and Ophthalmologic Drug Products (HFD-550), to review the proprietary name Acular — regarding potential name confusion with other proprietary/established drug names. The root name 'Acular' is the proprietary name for ketorolac tromethamine Ophthalmic Solution 0.5% which was approved November 9, 1992 (NDA# 19-700). The preservative free formulation, 'Acular PF, also contains ketorolac tromethamine 0.5% and was approved November 3, 1997 (NDA# 20-811). The proposed product, Acular — will contain ketorolac tromethamine 0.4% and will also contain the same preservative and inactive ingredients found in Acular. However, the indication of use differs from Acular. Acular is indicated for the temporary relief of itching due to seasonal allergic conjunctivitis, and for the treatment of postoperative inflammation in patients who have undergone cataract extraction whereas Acular — is indicated for reduction of ocular pain and ocular symptoms of foreign body sensation, photophobia, burning/stinging, and tearing following refractive surgery. The recommended dose of Acular — is one drop instilled in the operated eye four times a day for up to four days. Acular — will be marketed in 5 mL — dropper bottles. The draft container labels, carton and package insert labeling were reviewed for possible interventions to minimize medication errors.

II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts[1] as well as several FDA databases[2] for existing drug names which sound-alike or look-alike to "Acular — to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent

[1] Facts and Comparisons, 2003, Facts and Comparisons, St. Louis, Mo. http://www.efactsweb.com/index.asp MICROMEDEX Integrated Index, 003, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems and PDR/Physician's Desk Reference (Medical Economics Company Inc, 2003).

[2] The Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, New Drug Approvals 98-03, and the electronic online version of the FDA Orange Book.

and Trademark Office's Text and Image Database was also conducted.[3] The Saegis[4] Pharma-In-Use database was searched for drug names with potential for confusion. An expert panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted three prescription analysis studies consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

A. EXPERT PANEL DISCUSSION

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name "Acular — Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. The members of this panel include DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. The Expert Panel identified Acular, Acular PF, and Ocuclear as having the potential for confusion with Acular —

2. DDMAC had objections to the use of the modifier — ' in the name Acular The modifier — ' implies the drug is superior to other treatment options.

Table 1
Potential Sound-Alike/Look-Alike Names Identified by DMETS Expert Panel

Product Name	Dosage form(s); Established name	Usual adult dose*	Other**
Acular —	Ketorolac Tromethamine Ophthalmic Solution 0.4% 5 mL — ***Preservative:*** Benzalkonium Chloride 0.006% ***Inactive Ingredients:*** Edetate Disodium 0.015% Octoxynol 40, Purified Water, Sodium Chloride, Hydrochloric Acid and/or Sodium Hydroxide	One drop in the eye(s) operated on four times a day for up to four days	N/A
Acular	Ketorolac Tromethamine Ophthalmic Solution 0.5% 3 mL, 5 mL, and 10 mL Bottles ***Preservative:*** Benzalkonium Chloride 0.01% ***Inactive Ingredients:*** Edetate Disodium 0.1% Octoxynol 40, Purified Water, Sodium Chloride, Hydrochloric Acid and/or Sodium Hydroxide	***Ocular Itching:*** One drop in the affected eye(s) four times a day ***Postoperative Inflammation:*** One drop applied to the affected eye(s) four times a day for 2 weeks	LA/SA
Acular PF	Ketorolac Tromethamine Ophthalmic Solution 0.5% 0.4 mL Single Use Vials	One drop in the affected eye(s) four times a day as needed for pain and photophobia for up to three days	LA/SA
OcuClear (Over-the-Counter)	Oxymetazoline Ophthalmic Solution 0.025% 30 mL Bottles	One to two drops in affected eye(s) two to four times daily	SA

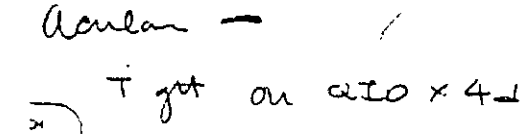
* Frequently used, not all-inclusive.
** L/A (look-alike), S/A (sound-alike)

[3] WWW location http://www.uspto.gov/main/trademarks.htm
[4] Data provided by Thomson & Thomson's SAEGIS ™ Online Service, available at www.thomson-thomson com

B. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

Three separate studies were conducted within FDA for the proposed proprietary name to determine the degree of confusion of Acular — with other U.S. drug names due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 131 health care professionals (pharmacists, physicians, and nurses). This exercise was conducted in an attempt to simulate the prescription ordering process. An inpatient order and outpatient prescriptions were written, each consisting of a combination of marketed and unapproved drug products and a prescription for Acular — (see below). These prescriptions were optically scanned and one prescription was delivered to a random sample of the participating health professionals via e-mail. In addition, the outpatient orders were recorded on voice mail. The voice mail messages were then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

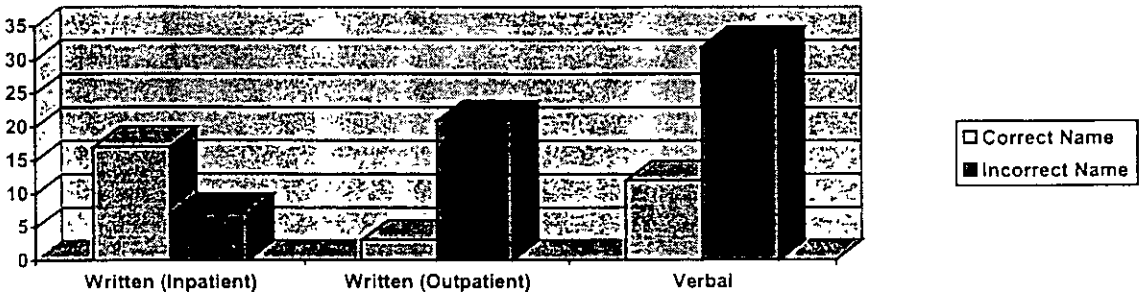
HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
Outpatient RX: Acular — 	The second is for Acular — Instill 1 drop 4 times a day to both eyes for 4 days. Dispense #1.
Inpatient RX: Acular — 1 gtt OU QID x 4d	

2. Results:

The results are summarized in Table I.

Table I

Study	# of Participants	# of Responses (%)	Correctly Interpreted	Incorrectly Interpreted
Written Inpatient	39	24 (62%)	17 (71%)	7 (29%)
Written Outpatient	35	24 (69%)	3 (13%)	21 (87%)
Verbal	57	44 (77%)	12 (27%)	32 (73%)
Total	131	92 (70%)	32 (35%)	60 (65%)



In the verbal study 12 of 44 (27%) participants interpreted Acular — correctly. The majority of the incorrect name interpretations were phonetic variations of "Acular — The majority of the misinterpretations include Acular PRE (5), Acular PM (4), Acular PR (3), Acular PN (3), Accular — 4). Single incorrect misinterpretations were Aculan Pn, Acculab — Acrolyte —, Acualr PN, Aculan PM, and Acula — Three participants correctly identified the root name, Acular, but omitted the modifier.

In the written outpatient prescription study 3 of the 24 (13%) participants interpreted Acular — correctly. The majority of the participants interpreted the root name correctly (Acular) but misinterpreted the modifier. The incorrect responses were Acular PM (5), Acular PN (5), Acular PRE (5), and Acular PR (3). Additionally, three respondents interpreted the root name correctly but did not include the modifier.

In the written inpatient study 17 (71%) of the 24 participants interpreted Acular — correctly. The remaining seven responses included correct interpretations of the root name Acular without including a modifier.

In all three studies, respondents interpreted the name as 'Acular' which, is a currently marketed and approved product.

3. SAFETY EVALUATOR RISK ASSESSMENT

a. Look-Alike and Sound-Alike Names

In reviewing the proprietary name Acular — the primary concerns raised were related to sound and/or look-alike names that currently exist in the US market: Acular, Acular PF, and OcuClear.

DMETS conducted prescription studies to simulate the prescription ordering process. There was no confirmation that Acular — could be confused with Acular PF, however the prescription studies confirmed that Acular — could be confused with Acular. Although there are limitations to the predictive value of these studies, primarily due to the small sample size, we have acquired safety concerns due to the positive interpretation with this drug product. A positive finding in a study with a small sample size may indicate a high risk and potential for medication errors when extrapolated to the general U.S. population. The majority of the misinterpretations from the verbal and written prescription studies were phonetic misinterpretations or spelling variations of the drug name Acular —

A search of the Adverse Event Reporting System (AERS) using the Preferred Terms 'Medication Error' and 'Overdose NOS' and drug names 'Acular' and 'Acul%' identified four cases. Two of the cases involved name confusion (see Attachment 1 for the full narratives). The first report dealt with *potential* name confusion between Acular and the word 'ocular.' The second report involved a *potential* medication error due to name confusion between the established names Ketorolac and Ketotifen. However, there is insufficient evidence at this time to conclude that the root proprietary name Acular has significant potential for name confusion. DMETS will continue to monitor post-marketing medication error reports in association with the proprietary name Acular.

There is potential for look and sound-alike confusion between Acular PF and Acular — because of the commonality of the root name, Acular, and the similarity between the modifiers, PF and — These products have overlapping dosing intervals (QID), routes of administration (ophthalmic), dosage forms (solution), and amount to be administered (one drop). The products are available in different strengths (0.5% vs. 0.4%) and have different indications of use. Both modifiers begin with the same letter. If the modifier is not clearly written and is misinterpreted the potential for errors increase especially since other product characteristics overlap. Additionally, the vial size of Acular PF and the strength of Acular — share similar numerical characters (i.e., 0.4). Confusion may occur if the strength (0.4%) of Acular — is misinterpreted as the vial volume (0.4 mL) of Acular PF. Unfortunately, prescribers do not always include the units of measure when writing prescriptions for products that are only available in a single strength thus increasing the potential for misinterpretation. Below are examples of ambiguous Acular — and Acular PF prescriptions, which may lead to misinterpretation of the prescription by the practitioner. If a patient receives Acular 0.5% in lieu of Acular 0.4%, the patient may experience stinging or burning upon instillation of the drug in the eye. Other adverse events found with the use of Acular 0.5% include corneal ulcer, eye dryness, headaches, and visual disturbance (blurry vision). In contrast a patient receiving Acular 0.4% instead of Acular 0.5% may experience conjunctival hyperemia, eye edema, eye pain, and headache. The similarities in the root proprietary names, the modifiers, and overlapping product characteristics increase the potential for medication errors due to name confusion.

ACULAR PF

ACULAR —

Ocuclear and the root name Acular may sound-alike depending upon how they are pronounced. The beginning letters of each name are phonetically similar (Ah-que). Additionally, both names end with the same letters (ar) which also increases the sound-alike similarities. However, the last syllable of Ocuclear (clear) is phonetically different than the last syllable of Acular (lar). Moreover, the use of the modifier — helps to distinguish the name. The products have overlapping dosage forms (solution), routes of administration (ophthalmic), dosing interval (every six hours vs.

QID), and amount to be administered (one drop). Ocuclear is available as an over-the-counter product whereas Acular [redacted] is a prescription only product. Although Ocuclear and Acular [redacted] have similar product characteristics, to date here have not been any reports of name confusion between the root name Acular and Ocuclear. Therefore, the potential for name confusion between these two products is minimal.

b. Modifier Concerns

Both Acular and Acular [redacted] have identical active and inactive ingredients, albeit different concentrations (0.5% vs. 0.4%). The only other differences between the two products are the indication of use and duration of treatment. We believe that the introduction of another strength of a prescription product can be effectively managed under a single proprietary name (Acular) where the prescriber must use a strength (0.4% or 0.5%) when prescribing the prescription. The sponsor has failed to submit a persuasive public health argument why a separate proprietary name/modifier is necessary for this new strength. We also recognize that an educational campaign must be implemented upon launch of this product so practitioners will be informed of the two different strengths and the appropriate uses of the product. The use of a modifier to indicate a different strength or indication of use may be confusing to practitioners and may increase the potential for medication errors. Modifiers are generally used to differentiate distinguishing characteristics (e.g., formulation) of products. A modifier is not necessary with this proprietary name since the two products do not have different product characteristics that need to be differentiated other than the strength and indications of use.

An additional concern is that the modifier [redacted] may be misleading to practitioners. Practitioners may interpret the modifier [redacted] as representing an Acular product that is either more effective or a product that provides a safer adverse event profile. The various indications of use do not indicate that Acular [redacted] is more effective or safer than Acular and Acular PF. In actuality the strength, of Acular [redacted] is lower than the currently marketed products (i.e., Acular and Acular PF) which may only contribute to potential confusion.

The modifier ' [redacted] ' should not be used with the proprietary name Acular to differentiate ketorolac tromethamine 0.5% from ketorolac tromethamine 0.4%. The two strengths of Acular should be differentiated by use of the strength (i.e., Acular 0.5% and Acular 0.4%). The container labels and carton labeling for Acular should be differentiated by highlighting with a different color or border or some other means.

c. Net Quantity

DMETS questions the rational of providing [redacted] of solution when the product is indicated for only four days.

III. COMMENTS TO THE SPONSOR

DMETS does not recommend the use of the proprietary name, Acular — Additionally, DMETS recommends no modifier be used for Acular to distinguish the different strengths and indications of use. Acular PF was identified as a potential sound and/or look-alike proprietary name to Acular —

a. Sound-alike and Look-alike Issues

There is potential for look and sound-alike confusion between Acular PF and Acular — because of the commonality of the root name, Acular, and the similarity between the modifiers, PF and — These products have overlapping dosing intervals (QID), routes of administration (ophthalmic), dosage forms (solution), and amount to be administered (one drop). The products are available in different strengths (0.5% vs. 0.4%) and have different indications of use. Both modifiers begin with the same letter. If the modifier is not clearly written and is misinterpreted the potential for errors increase especially since other product characteristics overlap. Additionally, the vial size of Acular PF and the strength of Acular — share similar numerical characters (i.e., 0.4). Confusion may occur if the strength (0.4%) of Acular — is misinterpreted as the vial volume (0.4 mL) of Acular PF. Unfortunately, prescribers do not always include the units of measure when writing prescriptions for products that are only available in a single strength thus increasing the potential for misinterpretation. Below are examples of ambiguous Acular — and Acular PF prescriptions, which may lead to misinterpretation of the prescription by the practitioner. If a patient receives Acular 0.5% in lieu of Acular 0.4%, the patient may experience stinging or burning upon instillation of the drug in the eye. Other adverse events found with the use of Acular 0.5% include corneal ulcer, eye dryness, headaches, and visual disturbance (blurry vision). In contrast a patient receiving Acular 0.4% instead of Acular 0.5% may experience conjunctival hyperemia, eye edema, eye pain, and headache. The similarities in the root proprietary names, the modifiers, and overlapping product characteristics increase the potential for medication errors due to name confusion.

ACULAR PF

ACULAR —

b. Modifier Concerns

Both Acular and Acular —have identical active and inactive ingredients, albeit different concentrations (0.5% vs. 0.4%). The only other differences between the two products are the indication of use and duration of treatment. We believe that the introduction of another strength of a prescription product can be effectively managed under a single proprietary name (Acular) where the prescriber must use a strength (0.4% or 0.5%) when prescribing the prescription. The sponsor has failed to submit a persuasive public health argument why a separate proprietary name/modifier is necessary for this new strength. We also recognize that an educational campaign must be implemented upon launch of this product so practitioners will be informed of the two different strengths and the appropriate uses of the product. The use of a modifier to

indicate a different strength or indication of use may be confusing to practitioners and may increase the potential for medication errors. Modifiers are generally used to differentiate distinguishing characteristics (e.g., formulation) of products. A modifier is not necessary with this proprietary name since the two products do not have different product characteristics that need to be differentiated other than the strength and indications of use.

An additional concern is that the modifier [redacted] may be misleading to practitioners. Practitioners may interpret the modifier [redacted] as representing an Acular product that is either more effective or a product that provides a safer adverse event profile. The various indications of use do not indicate that Acular [redacted] is more effective or safer than Acular and Acular PF. In actuality the strength, of Acular [redacted] is lower than the currently marketed products (i.e., Acular and Acular PF) which may only contribute to potential confusion.

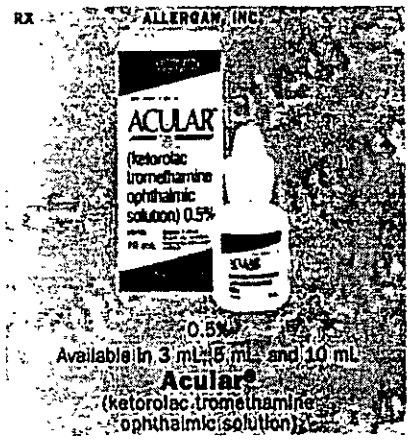
The modifier [redacted] should not be used with the proprietary name Acular to differentiate ketorolac tromethamine 0.5% from ketorolac tromethamine 0.4%. The two strengths of Acular should be differentiated by use of the strength (i.e., Acular 0.5% and Acular 0.4%). The container labels and carton labeling for Acular should be differentiated by highlighting with a different color or border or some other means.

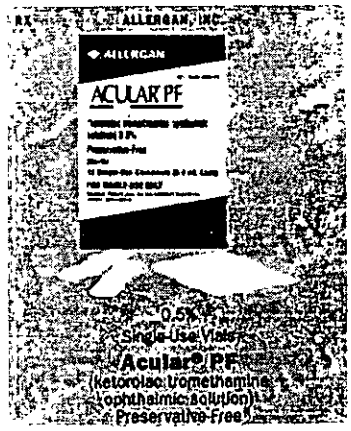
c. Net Quantity

DMETS questions the rational of providing [redacted] of solution when the product is indicated for only four days.

d. Label and Labeling Concerns

The Acular l [redacted] labels and labeling were submitted in draft format, which did not allow for a comprehensive evaluation of the color, format, etc. However, we note with the approval of Acular [redacted] the sponsor will market three Acular products with several similarities (e.g., indications of use and dosing schedules). The current presentation of Acular and Acular PF are very similar as noted below. DMETS recommends that the container labels and carton labeling of Acular [redacted] be clearly differentiated using boxing, color, font, and other means to help distinguish the products.





IV. RECOMMENDATIONS:

A. DMETS does not recommend the use of the modifier [redacted] in conjunction with the proprietary name, Acular for this 0.4% formulation of Ketorolac Tromethamine. Additionally, DMETS does not recommend use of any modifier in conjunction with Acular Ophthalmic Solution 0.4%.

B. DMETS recommends that the sponsor provide an educational campaign to health care practitioners upon launch of the new strength.

C. DMETS also recommends implementation of the labeling revision outlined in Section III of this review.

D. DDMAC does not recommend use of the proprietary name Acular [redacted] from a promotional perspective for the following reason: [redacted] implies the drug is superior to other treatment options.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Sammie Beam, project manager, at 301-827-3242.

Denise P. Toyer, Pharm.D.
Safety Evaluator/Team Leader
Division of Medication Errors and Technical Support

APPEARS THIS WAY
ON ORIGINAL

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/s/

Denise Toyer
4/24/03 04:24:27 PM
PHARMACIST

Carol Holquist
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Jerry Phillips
4/25/03 09:03:08 AM
DIRECTOR

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Form Approved OMB No 0910-0297
Expiration Date: February 29, 2004

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: http://www.fda.gov/cder/pdufa/default.htm

1. APPLICANT'S NAME AND ADDRESS

Allergan, Inc.
2525 Dupont Drive
P.O. Box 19534
Irvine, CA 92623-9534

2 TELEPHONE NUMBER *(Include Area Code)*

(800) 347-4500

4 BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER

N021528

5 DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?

☒ YES ☐ NO

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM

IF RESPONSE IS 'YES', CHECK THE APPROPRIATE RESPONSE BELOW

☒ THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION

☐ THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:

(APPLICATION NO. CONTAINING THE DATA)

3 PRODUCT NAME

Ketorolac Tromethamine Ophthalmic Solution 0.4%

6 USER FEE I.D. NUMBER

4381

7 IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION

☐ A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92
(Self Explanatory)

☐ A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE
(See item 7, reverse side before checking box.)

☐ THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act
(See item 7, reverse side before checking box.)

☐ THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act
(See item 7, reverse side before checking box.)

☐ THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY
(Self Explanatory)

8 HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION?

☐ YES ☒ NO

(See item 8, reverse side if answered YES)

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SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
Elizabeth Bancroft	Senior Director, Regulatory Affairs	23 July 2002

FORM FDA 3397 (4/01)

PATENT CERTIFICATION

I, the undersigned, hereby declare that Patent Nos. 4,454,151 and 5,110,493 cover the use/composition and formulation of Ketorolac Tromethamine Ophthalmic Solution 0.4%, the product for which approval is being sought. Allergan, Inc. has exclusive rights to both of these patents by agreement with the patents owner, Syntex (U.S.A.) L.L.C., a Delaware corporation. Because Patent No. 4,454,151 expires in September 2002, it will not be listed on the proposed labeling for Ketorolac Tromethamine Ophthalmic Solution 0.4% in application NDA 21-528.

ALLERGAN, INC.

By: _____ August 2, 2002

Martin A. Voet
Senior Vice President, Chief Intellectual
Property Counsel and Assistant Secretary

Date

APPEARS THIS WAY
ON ORIGINAL

United States Patent [19]
Waterbury

[11] **4,454,151**
[45] **Jun. 12, 1984**

[54] **USE OF PYRROLO PYRROLES IN TREATMENT OF OPHTHALMIC DISEASES**

[75] Inventor: **L. David Waterbury**, San Mateo, Calif.

[73] Assignee: **Syntex (U.S.A.) Inc.**, Palo Alto, Calif.

[21] Appl. No.: **360,754**

[22] Filed: **Mar. 22, 1982**

[51] **Int. Cl.**³ **A61K 31/40**
[52] **U.S. Cl.** **424/274**
[58] **Field of Search** 424/274

[56] **References Cited**

U.S. PATENT DOCUMENTS

4,087,539	5/1978	Muchowski et al.	424/274
4,089,969	5/1978	Muchowski et al.	424/274
4,097,579	6/1978	Muchowski et al.	424/274
4,140,698	2/1979	Van Horn et al.	424/274
4,232,038	11/1980	Kluge et al.	424/274
4,344,943	8/1982	Muchowski et al.	424/274

Primary Examiner—Douglas W. Robinson
Attorney, Agent, or Firm—Hana Dolezalova; Tom M. Moran; Alan M. Krubiner

[57] **ABSTRACT**

Certain known pyrrolo pyrroles have been found to be useful in the topical treatment of various ophthalmic diseases in mammals; especially those originating from or associated with inflammation such as, for example, cystoid macular edema, glaucoma, conjunctivitis, uveitis, diabetic retinopathy and eye surgery or trauma.

18 Claims, No Drawings

USE OF PYRROLO PYRROLES IN TREATMENT OF OPHTHALMIC DISEASES

BACKGROUND OF THE INVENTION

1. Field of the Invention

This invention relates to a method for the treatment of ophthalmic diseases originating from or associated with inflammation.

2. Related Disclosure

Many ophthalmic diseases are ocular disorders which are either caused or associated with painful inflammatory complications. Such complications very often lead to an impairment of the eyesight or blindness. Among those considered most dangerous belong glaucoma, cystoid macular edema, uveitis, diabetic retinopathy, conjunctivitis and postoperational or traumatic eye inflammation. When already developed all these ophthalmic diseases may be in acute, subacute or chronic form. The causes of ophthalmic inflammatory disorders may vary from bacterial, viral, fungal, parasitic, toxic, chemical, mechanical, irritative to allergic

Glaucoma is a group of ocular diseases with the common features of abnormally elevated intraocular pressure which slowly causes progressive loss of peripheral visual fields and then untreated, it causes a loss of central vision and ultimate blindness. The causes of the development of glaucoma are unknown. Glaucoma is usually treated topically by agents which contract the eye pupil such as pilocarpine or carbachol, systemically by osmotic agents or carbonic anhydrase inhibitors, or radically by surgery. *The Merck Manual*, 13th Ed., 1702, (1977).

Cystoid macular edema is a retinal edema which may result from cataract removal. A newly proposed theory of the cause of a cystoid muscular edema is a release of prostaglandins or other inflammatory mediators derived from a disrupted blood-aqueous barrier into the aqueous. This theory is supported by findings that it is possible to subdue cystoid macular edema by the pre- and/or post-operative application of topical indomethacin, known suppressant of elevated levels of prostaglandins. *Albrecht v. Graefes Arch. Klin. Exp. Ophthal.*, 209:83–88, (1978).

Uveitis is an inflammation of the uveal tract encompassing inflammation of the iris, ciliary body and choroid. Uveitis may also develop following trauma where the ciliary body was injured. Predominant objective of the treatment of uveitis is suppression of damaging inflammatory activity. Dexamethazone drops, short-term systemic corticosteroid treatment or photocoagulation of the lesions are most commonly used for the treatment of uveitis. *The Merck Manual*, 13th Ed., 1697, (1977).

Diabetic retinopathy is microcirculatory complication associated with progressive form of the diabetes mellitus. It is characterized by proliferative neovascularization in the posterior pole of the eye often extending into vitreous cavity with subsequent vitreous hemorrhages, fibrous formation, and secondary retinal detachment and thickening of the capillary basement membrane. Treatments used to relieve severe symptoms of diabetic retinopathy include the strict control of blood pressure or laser photocoagulation of proliferating neovascular tufts to reduce the degree of retinal edema and the frequency and severity of hemorrhagic episode *The Merck Manual*, 13th Ed., page 1700, (1977). In the pending application Ser. No. 162,355 applicants Ringold and Waterbury propose the systemic use of analgesics and non-hormonal anti-inflammatories in treatment of microvascular diseases.

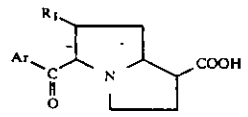
Conjunctivitis is an inflammation of the conjunctiva and a mucous membrane characterized by a cellular infiltration and exudation. Conjunctivitis may be either acute, where the conjunctival inflammation is caused by viruses, allergy or bacteria; or chronic, where the inflammation of the conjunctiva is characterized by exacerbations and remissions that occur over the period of months or years. The causes for chronic conjunctivitis are similar to those of acute conjunctivitis. The treatment of both acute and chronic conjunctivitis include the topical administration of sulfonamide drops, antibiotic ointments, or systemic antibiotic therapy. The most important prevention of chronic conjunctivitis is elimination of all irritating factors. In the case of allergic conjunctivitis, topical corticosteroid therapy is also indicated. *Merck Manual* 13th Ed., page 1687 (1977).

Other inflammatory complications of the eye are those developing after the direct injury to the dye or those caused by trauma during the eye surgery. Injuries to the eye may be caused by foreign bodies, lacerations, contusions, burns by chemicals, or others. The treatment of eye injuries and post-traumatic inflammations consists of anesthesia, precise diagnosis of the injury or trauma and post-traumatic or pre- or post-operative prevention of development of inflammation. *The Merck Manual*, 13th Ed., page 1680 (1977).

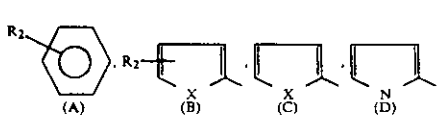
Compounds which are subject of this invention and those having similar structures to these compounds are known and have been described in U S Pat. Nos. 4,089,969, 4,232,038; 4,087,539 and 4,097,579. They are generally useful as a systemic anti-inflammatory, systemic analgesic and systemic antipyretic agents and smooth muscle relaxants. Their proposed uses as anti-inflammatories, antipyretics, analgesics or as a smooth muscle relaxants are in the form of tablets, capsules, suppositories, oral suspensions for systemic pediatric use or as a powdered top dressings for veterinary use These compounds were not previously administered topically, i.e., directly to the eye, to prevent or treat ophthalmic diseases probably because their non-irritating properties are unexpected and surprising.

SUMMARY OF THE INVENTION

This invention is a method for prevention or treating ophthalmic diseases in mammals, which method comprises administering directly to the eye of a mammal in need thereof a pharmaceutically effective amount of a compound of the formula



and the pharmaceutically non-toxic esters and salts thereof wherein Ar is

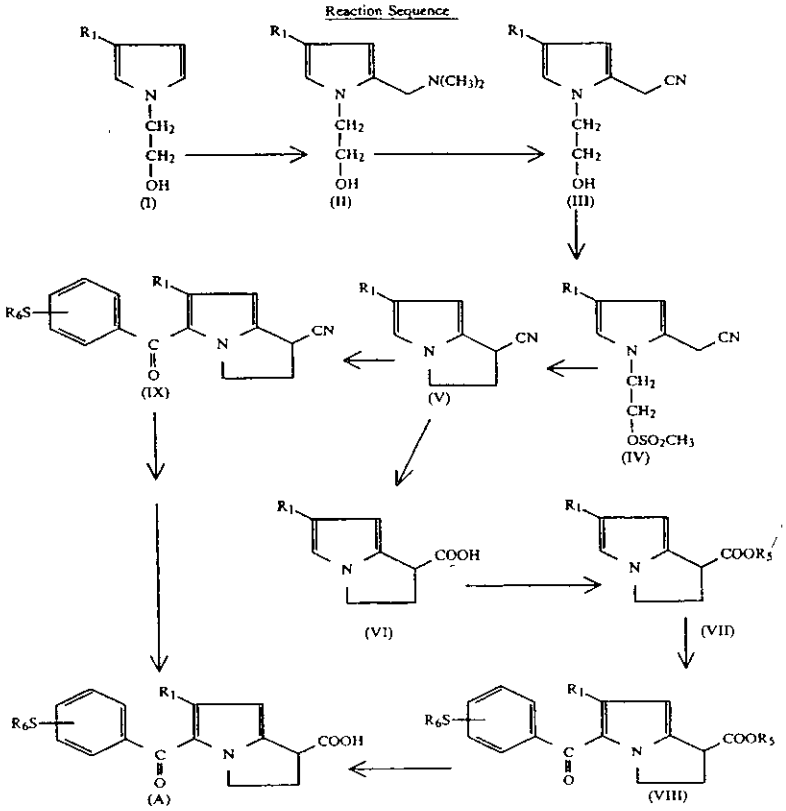


reference to the U S. Pat. No. 4,097,579 to Muchowski et al, issued in June 27, 1978.

Detailed description of the preparation of 5-alkylsulfinylbenzoyl- and 5-alkylsulfonylbenzoyl-2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylic acid compounds of Formula (A) and their pharmaceutically acceptable non-toxic esters and salts is hereby incorporated by reference to the U.S. Pat. No. 4,232,038 to Kluge et al, issued on Nov. 4, 1980.

5-alkylthiobenzoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylic acid compounds of Formula (A) are prepared by a process illustrated by the following reaction sequence.

Reaction Sequence



R_1 represents hydrogen; lower alkyl group having from one to four carbon atoms, chloro or bromo,

R_5 represents methyl, ethyl, isopropyl or n-butyl depending on whether methanol, ethanol, isopropanol or n-butanol are used for esterification;

R_6 represents alkyl;

The starting compound 2-aminoethanol acetate (not shown) is prepared by reacting 2-aminoethanol with glacial acetic acid at a temperature of between 5° and 50° C. This compound is then reacted with dimethoxytetrahydrofuran at reflux temperature for a period of time sufficient to give the desired pyrrole and the corresponding acetate. The reaction takes generally less than about 5 hours. After extracting the product from the reaction mixture, the mixture is hydrolyzed using a basic alcohol mixture such as sodium hydroxide and methanol at room temperature to give solely the desired product represented by formula (I).

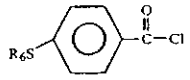
This in turn is reacted at slightly elevated temperatures, e.g 20°–60° C., with a solution of dimethylamine hydrochloride in aqueous formaldehyde to give 1-(2-hydroxyethyl)-2-dimethylaminomethylpyrrole (II). After extraction with a suitable organic solvent such as dichloromethane and subsequent purification by evaporation and distillation, the compound represented by Formula (II) is then dissolved in acetone and is maintained in an inert atmosphere using nitrogen or argon and a slight molar excess of dimethylsulfate is added to the cooled reaction mixture at such a rate that the temperature does not exceed about 5° C. When addition of the dimethylsulfate is completed, the solution is stirred at room temperature and a solution of sodium cyanide in water is added. The resulting reaction mixture is heated to reflux temperature, i.e. generally about 90°–100° C. and the distillate is collected. The reaction mixture is heated at a gentle reflux for a suitable period of time, generally less than 2 hours, preferably about ½ hour and water is added to the mixture After extracting, drying and purification by column chromatography, a nitrile represented by Formula (III) is obtained, namely 1-(2-hydroxyethyl)pyrrol-2-yl-acetonitrile.

The compound of Formula (III) is then converted to the corresponding 1-(2-methanesulfonyloxy)ethylpyrrol-2-yl-acetonitrile by esterification with methanesulfonyl chloride in the presence of a tertiary amine, i.e., triethylamine, pyridine and the like. Optionally, in the presence of a solvent such as dichloromethane, at a temperature from about −10° C. to about room temperature, for about 10 minutes to about 2 hours esterification produces the corresponding mesyl ester. The mesyl ester represented by Formula (IV) is converted to the corresponding 1-cyano-1,2-dihydro-3H-pyrrolo-[1,2-a]pyrrole of Formula (V). By reaction with sodium iodide in acetonitrile solution, at reflux temperature for from about 1 to about 10 hours. The preparation of the compound of Formula (V) is discussed in U.S. Pat. No. 4,100,698 to Van Horn et al and that patent is incorporated herein by reference.

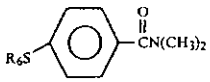
Nitrile of Formula (V) can be converted into the acid represented by Formula (VI) by reacting with aqueous sodium or potassium hydroxide in ethylene glycol at elevated temperatures of up to 120° C for a time sufficient for the reaction to take place, generally less than about 5 hours. Extracting the reaction mixture with a suitable organic solvent, bringing the aqueous phase to an acid pH by using concentrated hydrochloric acid and extracting from water, results in the acid represented by Formula (VI). The acid, in turn, is converted to the ester of Formula (VII) by reaction with a lower aliphatic alcohol in the presence of an acid such as hydrochloric acid.

The carboxylic acid group at the C-1 position in compound (VI) is selectively esterified by treatment with a lower aliphatic alcohol, e.g., methanol, ethanol, isopropanol, n-butanol and the like in the presence of hydrogen chloride, to produce the corresponding alkyl 1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylic acid of Formula (VII) The reaction is conducted at a temperature of from about 0° to about 50° C., for about 1 to about 4 hours.

A compound of Formula (VII) is then converted to the alkylthiobenzoyl compound of Formulas (VIII) and (A) by a condensation of a compound (VII) with either an acid chloride of the formula



or a reagent prepared from an amide of the formula



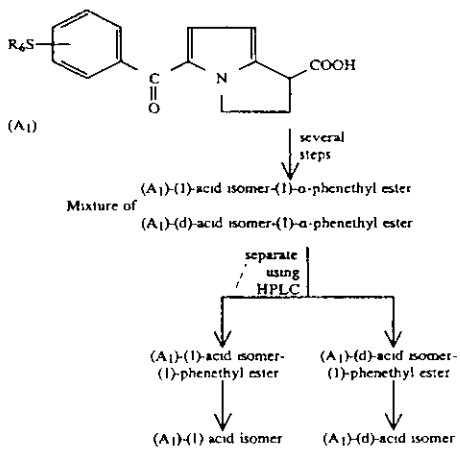
and phosphorus oxychloride wherein R_6 has the above-indicated meaning, affords the corresponding alkyl 5-benzoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylic acid (VIII). This is done following process conditions set forth in U S. Pat No 4,089,969.

In the preferred embodiment of this process, this condensation is carried out by adding a solution of compound of Formula (VII) in a suitable solvent to a previously refluxed mixture of 1.1 to 5 molar equivalents of both the desired amide and phosphorus oxychloride in the same solvent, refluxing the reaction mixture thus obtained for from about 6 to about 72 hours under an argon atmosphere and thereafter adding thereto from about 3 to about 10 molar equivalents of sodium acetate, followed by an additional reflux period for from about 4 to about 6 hours

Alternatively, the intermediate nitrile of Formula (V) can be converted into the nitrile of Formula (IX) in Reaction Scheme using reaction conditions discussed hereinbefore in the conversion of the compound of Formulas (VII) to (VIII). The compound of Formula (IX), in turn, is converted to a compound (A) of the invention by converting the nitrile moiety to an acid as discussed hereinbefore.

The compounds of Formula (A) can be resolved, according to methods known in the art, to obtain the corresponding individual isomers thereof.

The (l)-acid isomers and (d)-acid isomers of the compounds of Formula (A) can be obtained by applying the known technique of high pressure liquid chromatography (HPLC) to the α-phenethyl diastereoisomeric esters of the compounds of Formula (A), followed by acid cleavage. Thus, for example, the compounds of Formula (A) wherein R_1 and R_6 are both hydrogen can be subjected to further treatment in accordance with the following flow diagram:



The free acids of Formula (A), (B), (C) and (D) can be converted into other alkyl esters having from 1 to 12 carbon atoms by conventional methods, e.g., by treatment with (a) the alcohol corresponding to the desired ester in the presence of a strong mineral acid, (b) an ethereal diazoalkane or (c) the desired alkyl iodide in the presence of lithium carbonate.

The salt derivatives of the compounds of Formula (A), (B), (C) and (D) are prepared by treating these free acids with an appropriate amount of a pharmaceutically acceptable base. Representative pharmaceutically acceptable bases are sodium hydroxide, potassium hydroxide, lithium hydroxide, ammonium hydroxide, calcium hydroxide, magnesium hydroxide, ferrous hydroxide, zinc hydroxide, copper hydroxide, manganous hydroxide, aluminum hydroxide, ferric hydroxide, manganic hydroxide, isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, ethanolamine, 2-dimethylaminoethanol, 2-diethylaminoe-

thanol, tromethamine, lysine, arginine, histidine, caffeine, procaine, hydrabamine, choline, betaine, ethylenediamine, glucosamine, methylglucamine, theobromine, purine, piperazine, piperidine, N-ethyl-piperidine, polyamine resins and the like. The reaction is conducted in water, alone or in combination with an inert, water-miscible organic solvent, at a temperature of from about 0° to about 100° C., preferably at room temperature Typical inert, water-miscible organic solvents include methanol, ethanol, isopropanol, butanol, acetone, dioxane or tetrahydrofuran. The molar ratio of compounds of Formula (A), (B), (C) and (D) to base used are chosen to provide the ratio desired for any particular salt For preparing, for example, the calcium salts or magnesium salts of the compounds of Formula (A), (B), (C) and (D) the free acid starting material can be treated with at least one-half molar equivalent of pharmaceutically acceptable base to yield a neutral salt. When the aluminum salts of the compounds of Formula (A), (B), (C) and (D) are prepared, at least one-third molar equivalent of the pharmaceutically acceptable base are employed if a neutral salt product is desired

In the preferred procedure, the calcium salts and magnesium salts of the compounds of Formula (A), (B), (C) and (D) can be prepared by treating the corresponding sodium or potassium salts thereof with at least one-half molar equivalent of calcium chloride or magnesium chloride, respectively, in an aqueous solution, alone or in combination with an inert water-miscible organic solvent, at a temperature of from about 20° to about 100° C. Preferably, the aluminum salts of the compounds hereof, can be prepared by treating the corresponding free acids with at least one-third molar equivalent of an aluminum alkoxide, such as aluminum triethoxide, aluminum tripropoxide and the like, in a hydrocarbon solvent, such as benzene, xylene, cyclohexane and the like, at a temperature of from about 20° to about 115° C. Similar procedures can be used to prepare salts of inorganic bases which are not sufficiently soluble for easy reaction.

The salt derivatives of the compounds of formula (A), (B), (C) and (D) can be reconverted to their respective free acids by acidifying said salts with an acid, preferably an inorganic acid, e g , hyrochloric acid, sulfuric acid, and the like, at temperature of from about 0° C to about 50° C., preferably at room temperature.

The pharmaceutically acceptable non-toxic esters of formula (A), (B), (C) and (D) are prepared by esterifying the corresponding free acids with an alcohol reagent corresponding to the desired ester, e.g., an alkanol having up to 12 carbon atoms or with glycerol which is already esterified at two hydroxyls to other suitable acids. This reaction is conducted in the presence of a strong acid, such as boron trifluoride, hydrogen chloride, sulfuric acid, p-toluenesulfonic acid, and the like. If the alcohol reagent used in the esterification is a liquid at the reaction temperature, the alcohol reagent can be the reaction solvent Optionally, the reaction can be carried out in an inert organic solvent in which the free acids and the alcohol reagent are soluble, such as a hydrocarbon solvent, e.g , hexane, isooctane, decane, cyclohexane, benzene, toluene, xylene, a halogenated hydrocarbon solvent, e.g., methylene chloride, chloroform, dichloroethane, or an ether solvent, e g , diethyl ether, dibutyl ether dioxane, tetrahydrofuran, and the like In the case where the alcohol reagent is a solid, the reaction preferably is conducted in a non-aqueous liquid inert organic solvent The reaction is conducted at from about 0° C. to the reflux temperature of the reaction mixture, preferably using hydrogen chloride at a temperature of from 15° C to about 35° C.

The product is isolated by conventional means such as diluting the reaction mixture with water, extracting the resulting aqueous mixture with a water-immiscible inert organic solvent, such as diethyl ether, benzene, methylene chloride, and the like, combining the extracts, washing the extracts with water to neutrality and then evaporating under reduced pressure.

Typical esters are those ester derivatives prepared from methyl alcohol, ethyl alcohol, propyl alcohol, isopropyl alcohol, butyl alcohol, 2-butyl alcohol, 2-pentyl alcohol, isopentyl alcohol, 2-hexyl alcohol, and the like.

Alternatively, the alkyl esters can be prepared by transesterification, according to methods known in the art. It is preferred in preparing the esters via transesterification to go from a lower ester to a higher ester, e.g., from the methyl ester, for example, to the isoamyl ester, for example However, by using a substantial excess of a lower alcohol, a higher ester can be transesterified to a lower ester; thus, for example, by using a substantial excess of ethanol, the hexyl ester is converted by the transesterification to the ethyl ester.

It is to be understood that isolation of the compounds described herein can be effected, if desired, by any suitable separation or purification procedure, such as for example, extraction, filtration, evaporation, distillation, crystallization, thin-layer chromatography or column chromatography, high pressure liquid chromotography (HPLC) or a combination of these procedures

The novel compounds of Formula (A), (B), (C) and (D) depicted above exist as pairs of optical isomers (or enantiomorphs), i e , a (dl) mixture. However, each optical isomer as well as the (dl) mixtures thereof are included within the present invention.

While the (d)-acid isomers are not used as a medicinal of agents per se, they can, if desired, be converted to their pharmaceutically acceptable, nontoxic esters and salts thereof according to the methods described for the conversion of the (1-) acid isomers to their pharmaceutically acceptable, nontoxic esters and salts thereof.

Utility and Administration

This invention is directed to method useful for relieving, inhibiting or preventing ophthalmic diseases in mammals These diseases may be, among others, glaucoma, cystoid macular edema, uveitis, diabetic retinopathy, conjunctivitis or any trauma caused by eye surgery or eye injury and which are either caused by, associated with, or accompanied by inflammatory processes.

The method of this invention is both curative and preventative Where applied, for example, pre-surgically or immediately post-traumatically, i e. before inflammation develops, it prevents development of inflammation. When applied directly to the eye suffering from any of the named ophthalmic diseases, it supresses already developed inflammatory processes. Thus, for example, a topical application of appropriate ophthalmic solution with active ingredient to the eye suffering from glaucoma, will not only stop further increase in intraoccular pressure but it will also descrease the pressure to its normal level

The human eye is an excellent subject for the topical administration of drugs The basis of this can be found in the anatomical arrangement of the surface tissues and

in the permeability of the cornea. The protective operation of the eyelids and lacrimal system is such that there is rapid removal of material instilled into the eye, unless the material is chemically and physiologically compatible with surface tissues.

The optical apparatus consists, in sequence, of the cornea, the pupil, and the crystalline lens, with layers of clear fluid or gel-like material interposed between the solid structures The pupil, a round centric hole in a contractile membranous partition (called the iris), acts as the variable aperture of the system. The crystalline lens is a refractive element with variable power controlled and supported by a muscle incorporated in the ciliary body. The chloroid is the metabolic support for the retina.

The optical function of the eye calls for the stability of its dimensions which is provided partly by the fibrous outer coat; more effective as a stabilizing factor is the intraocular pressure which is in excess of the pressure prevailing in the surrounding tissues. This intraocular pressure is the result of a steady production of specific fluid, the aqueous humor, which originates from the ciliary processes and leaves the eye by an intricate system of outflow channels. The resistance encountered during this passage and the rate of aqueous production are the principal factors determining the level of the intraocular pressure In addition to this hydromechanical function, the aqueous humor acts as a carrier of nutrients, substrates, and metabolites for the avascular tissues of the eye

The conjunctival membrane covers the outer surface of the white portion of the eye and the inner aspect of the eyelids In most places it is loosely attached and thereby permits free movement of the eyeball. This makes possible subconjunctival injections. Except for the cornea, the conjunctiva is the most exposed portion of the eye; thus, the most susceptible to infection.

The conjunctival and corneal surfaces are covered and lubricated by a film of fluid secreted by the conjunctival and the lacrimal glands The secretion of the lacrimal gland, the tears, is delivered through a number of fine ducts into the conjunctival fornix The secretion is a clear, watery fluid containing 0 7% protein and the enzyme lysozyme Small accessory lacrimal glands are situated in the conjunctival fornices. Their secretion suffices for lubrication and cleansing under ordinary conditions and for maintaining a thin fluid film covering the cornea and conjunctiva (the precorneal film).

The cornea is transparent anterior portion of the outer coat of the eye. The normal cornea possesses no blood vessels except at the corneoscleral junction The cornea, therefore, must derive its nutrition by diffusion and must have certain permeability characteristics, it also receives nourishment from the fluid circulating through the chambers of the eye and also from the air.

Cloudiness of the cornea may be due to any one of several factors including excess pressure in the eyeball (as in glaucoma); scar tissue (due to injury or infection), or deficiency of oxygen or excess hydration (as may occur during the wearing of improperly fitted contact lenses). A wound of the cornea usually heals as an opaque patch which may result in a permanent disability unless it is located in the periphery of the cornea.

The corneal epithelium provides an efficient barrier against bacterial invasion Unless its continuity has been broken by an abrasion (a traumatic opening or defect in the epithelium) pathogenic bacteria, as a rule, cannot gain a foothold. Trauma, therefore, plays an important part in most of the infectious diseases of the cornea which occur exogenously. Any foreign body which either scratches the cornea or lodges and becomes imbedded in the cornea is of serious moment because of the role it may play in permitting pyogenic bacteria to gain a foothold.

The therapeutic effect of many topically administered (instilled) drugs is contingent upon their absorption from the cul-de-sac into the eye. Drugs which are administered by instillation and which must penetrate into the eye enter primarily through the cornea. This is a much more effective route of administering the drug into the eye than through the conjunctiva and underlying sclera.

The conjunctiva contains many blood vessels and lymphatic vessels. The blood vessels usually dilate when irriation is set up by a foreign body, a microbial infection, or by chemical means. Of the drug molecules which penetrate into the conjunctiva a large proportion enters the blood stream where they may cause undesirable systemic reactions. Below the conjunctiva lies the sclera, which water-soluble drugs penetrate with ease and which lipoid-soluble drugs penetrate with difficulty.

In the non-inflamed eye, the blood-aqueous barrier, constituted of the blood vessel wall and various thicknesses of the ocular tissues, prevents certain drugs from reaching the anterior segment in therapeutic concentrations if administered systemically.

In the inflamed eye permeability of the blood-aqueous barrier is increased, allowing few drugs administered systemically in therapeutic quantities to reach the anterior chamber of an inflamed eye, but many more drugs will have such effect only if administered systemically in quantities that would cause harm in other parts of the body. In general, in the treatment of the anterior segment of the eye, such systemic administration does not accomplish as much as topical administration.

The compounds of Formulas (A), (B), (C) and (D) and their pharmaceutically acceptable non-toxic alkyl esters and salts (described hereinabove) have been found, in animal experiments, to be non-irritating, hence physiologically compatible, and yet to have a profound antiinflammatory effect when applied directly to the eye. Thus, these compounds are highly potent in penetrating ocular tissue but, surprisingly, upon their topical application, they show no irritation of the ocular tissue Compounds of this invention show considerable biological activities effecting especially neovascularization experimentally induced by silver nitrate, uveitis experimentally induced by endotoxin, or glaucoma-like increase in intraoccular pressure induced by arachidonic acid. Accordingly, these compounds, when applied topically, offer a method for treating ocular disorders caused or associated with inflammatory processes of the mammalian eye without exposing the mammal to the danger of secondary symptoms caused by large dosages required for systemic treatment.

In the practice, the compounds of the invention or their pharmaceutically acceptable non-toxic alkyl esters and salts are administered topically, i.e., directly to the eye of a subject suffering from inflammatory complications of the eye. Administration is in the form of ophthalmic preparation applied directly to the eye

Ophthalmic preparations are sterile products for either topical application to the eyelids or instillation into the space (cul-de-sac) between the eyeball and the eyelids. Presently available ophthalmic preparations in-

clude solutions, suspensions, and ointments. Presently available topical treatment of eye diseases include topically applied ophthalmic drops, solutions, suspensions or ointment or their subconjunctival injection.

Most ophthalmic solutions are so formulated as to mix readily with the lacrimal fluids and spread over the surfaces of the cornea and conjunctiva. With the usual technique of installation the major portion of the drug is deposited in the lower fornix. Capillarity, diffusional forces, and the blinking reflex are the forces that bring about the incorporation of the drug in the precorneal film from which it penetrates into and through the cornea

Studies have indicated that a substance will pass through the cornea most easily if it has a biphasic solubility; that is, if it is soluble both in fat and in water

The cornea can be penetrated by ions to a small, but measurable, degree. Under comparable conditions, the permeabilities are similar for all ions of small molecular weight, which suggests that the passage is through the extracellular spaces. The diameter of the largest particles which can pass across the cellular layers seem to be in the range of 10–25 Å. Increase in the permeability of the cellular layers can be produced by experimental techniques which involve slight manipulations such as touching the cornea, or instilling solutions differing in tonicity from that of the body fluids, or even stirring the solution in contact with the corneal surface.

The composition of this invention comprises, as active ingredient, a compound of formula (A), (B), (C) or (D) or an ester or salt thereof as described hereinabove, in admixture with an ophthalmologically acceptable excipient. An excipient is ophthalmologically acceptable if it is non-irritating to the eye and if its active ingredient penetrates the blood-aqueous barrier and/or difuse to or through the various ocular substructures to the site where it is pharmacologically active. The composition may be and may be aqueous or non-aqueous, on the form of a solution, suspension, gel, ointment, slow release polymer, or other. Amount of active ingredient will vary with the particular formulation and disease state but generally will be betweeen 0.001–10 percent of active ingredient per individual application dose.

Pharmaceutical ophthalmic compositions are typically sterilized aqueous solutions (i.e. eyedrops) containing 0 001% to 10% wt/vol.; most preferably 0 005% to 1% of the active ingredient, along with suitable buffer, stabilizer, and preservative The total concentration of solutes should be such that, if possible, the resulting solution is isotonic with the lacrimal fluid (though this is not absolutely necessary) and has an equivalent pH in the range of pH 6-8 Typical preservatives/sterilants are phenylmercuric acetate, thimerosal, chlorobutanol, and benzalkonium chloride. Typical buffer systems and salts are based on, for example, citrate, borate or phosphate; suitable stabilizers include glycerin and polysorbate 80. The aqueous solutions are formulated simply by solutes in a suitable quantity of water, adjusting the pH to about 6.8–8.0, making a final volume adjustment with additional water, and sterilizing the preparation using method known to those in the art.

The dosage level of the resulting composition will, of course, depend on the concentration of the drops, the condition of the subject and the individual magnitude of responses to treatment However, typical dosage ranges might be about 2–10 drops of 0 1% solution of active ingredient per day.

Most ophthalmic solutions and suspensions contain an aqueous rather than an oily vehicle. Ophthalmic ointments usually contain a white petrolatam-mineral oil base, often including anhydrous lanolin, while some have a polyethylene-gelled mineral oil base.

Solutions are the most commonly used type of preparation for the local medication of eyes. They are easily instilled and rarely cause adverse reactions. The vehicle does not cause interference with vision and does not interfere with regeneration of the corneal epithelium

Oily solutions such as for medicaments which are incompatible with water are infrequently used. The only official ophthalmic solution using oil is that of isoflurophate.

Suspensions have the advantage of more extended action and the disadvantage that it is difficult to avoid the presence of a few particles which are large enough to cause irritation

Eye ointments are sterile preparations for application to the conjunctival sac or lid margin. They have advantages of more prolonged contact and effect, hardly any irritation on initial installation, slower movement into lacrimal ducts, greater storage stability, and less likelihood of contamination problems. Their disadvantages are that they produce a film over the eye and thereby blur vision; and they may interfere with the firm attachment of new corneal epithelial cells to their normal base. Ointments affect the outside and edges of the eyelids, the conjunctiva, the cornea, and the iris, depending on their ability to penetrate the outer covering of the eyeball. Topical drugs can affect the anterior chamber (between the cornea and the iris), the ciliary body (part of which holds the lens and adjusts its shape), and the lens

Ophthalmic ointments comprising active ingredients can be used for the effect of a variety of medicaments on the outside and edges of the eyelids, the conjunctiva, the cornea, and the iris. Most ophthalmic ointments are prepared with a base of white or yellow petrolatum and mineral oil, often with added anhydrous lanolin. Whichever base is selected, it must be nonirritating to the eye, permit diffusion of the drug throughout the secretions bathing the eye, anbd retain the activity of the medicament for a reasonable period of time under proper storage conditions

A suitable basis for eye ointments is given by the following formula

Liquid Paraffin	100 g
Wool Fat	100 g
Yellow Soft Paraffin	800 g

The wool fat, the yellow soft paraffin and the liquid paraffin are heated together, filtered whie hot through a course filter paper in a heated funnel, sterilized by heating for a sufficient time to ensure that the whole of the basis is maintained at a temperature of 150° for one hour, and allowed to cool, taking precautions to avoid contamination with micro-organisms, before incorporating the sterile medicament.

Eye ointments are prepared, by means of an aseptic technique, by either of the following methods

Method A If the medicament is readily soluble in water forming a stable solution, it is dissolved in the minimum quantity of water and the solution sterilized by autoclaving or by filtration and incorporated gradually in the melted sterile basis, the mixture being stirred

continuously until it is cold The eye ointment is then transferred to the final sterile containers, which are closed so as to exclude micro-organisms.

Method B. If the medicament is not readily soluble in water or if the aqueous solution is unstable, the medicament is finely powdered, thoroughly mixed with a small quantity of the melted sterile basis, and then incorporated with the remainder of the sterile basis. The eye ointment is then transferred to the final sterile containers, which are closed so as to exclude microorganisms.

If the medicament is insoluble in both water and the basis, it is essential that it be reduced to an extremely fine powder before incorporating with the basis, in order to avoid irritation to the eye.

It is obligatory that ophthalmic ointments do not contain particulate matter that may be harmful to eye tissues. Hence, in preparing such ointments special precaution is taken to exclude or to minimize contamination with foreign particulate matter, e.g., metal particles fragmented from equipment used in preparing ointments, and also to reduce the particle size of the active ingredient(s) to impalpability. The official compendia provide tests designed to limit to a level considered to be unobjectionable the number and size of discrete particles that may occur in ophthalmic ointments. In these tests the extruded contents of tubes of ointment, previously melted in flat-bottom Petri dishes and then allowed to solidify, are scanned under a low-power microscope fitted with a micrometer eyepiece for (1) metal particles 50μ or larger in any dimension and (2) other particles 50μ or larger in any dimension The limit for each kind of particle is 50 in a total of 10 tubes of ointment and 8 in not more than 1 of the 10 tubes.

Testing for sterility of products such as ophthalmic ointments has been greatly facilitated by use of sterile bacteria-retaining membranes (those having a nominal porosity of 0 45μ are commonly used). For ointments soluble in isopropyl myristate (the solvent used in the official test for sterility) a sample of the ointment is dissolved in the sterile solvent and filtered through the sterile membrane which, after washing with sterile rinse medium, is subjected to the sterility test. For ointments insoluble in isopropyl myristate the sample is suspended in a suitable aqueous vehicle that may contain a dispersing agent.

For a long time the technology available for manufacture of ophthalmic ointments was not adequate to produce sterile products; indeed it was believed by some to be impossible to operate a tube-filling machine so as to maintain sterility even in a sterile room. In recent years technological advances have made is possible to manufacture sterile ophthalmic ointment units. Major improvement was achieved in the area of filtration technology. Membrane filters have improved and reliability of both sterile filtration procedures and sterility-testing methods. Use of laminar flow of HEPA-filtered air in appropriately designed rooms and hoods has been a major factor in the successful aseptic operation of the roller mill and of devices for filling tubes with ointment.

The official compendia direct that ophthalmic ointments be prepared from previously sterilized ingredients, under rigidly aseptic conditions. Petrolatum vehicles and many medicaments may be sterilized by heating in a hot-air oven at 150° C. for 2 hours; utensils required for compounding may be sterilized by autoclaving; empty tubes may be sterilized by storage for 24 hours in a 1:1000 solution of benzalkonium chloride in 70% isopropyl alcohol followed by removal of alcohol by evaporation. A sterile disposable syringe without a needle may be used to transfer the finished ointment, if it is semi-fluid, to the ointment tube, or sterile aluminum foil or powder paper may be used for the same purpose. Probability of microbial contamination is greatly reduced by carrying out selected steps of the procedure in a laminar-flow hood.

Compounds of this invention may also be administered by other nonsystemic modes. Ophthalmic packs may be used to give prolonged contact of the solution with the eye. A cotton pledget is saturated with an ophthalmologically suitable solution and this pledget is inserted into the superior or inferior fornix. Packs are commonly used to produce maximal mydriasis. In this case the cotton pledgets can be, for example, saturated with a solution of a compound of this invention. Medicated ophthalmic disks produce mitosis both more intense and prolonged than either solution. Use of disks may be preferable to use of solutions.

The compounds may also be administered by the way of iontophoresis. This procedure keeps the solution in contact with the cornea in an eyecup bearing an electrode. Diffusion of the drug is effected by difference of electrical potential

Subconjunctival injections of compounds of the current invention may be used to introduce medications which, if instilled, either do not penetrate into the anterior segment or penetrate too slowly for the desired effect The drug is injected underneath the conjunctiva and propably passes through the sclera and into the eye by simple diffusion The most common use of subconjunctival injection is for the administration of antibiotics in infections of the anterior segment of the eye Subconjunctival injections of mydriatrics and cycloplegics are also used to achieve maximal pupillary dilation or relaxation of the ciliary muscle. If the drug is injected underneath the conjunctiva and the underlying Tenon's capsule in the more posterior portion of the eye, effects on the ciliary body, choroid, and retina can be obtained

Drugs may also be administered by retrobulbar injection whereby they enter the globe in essentialy the same manner as the medications given subconjunctivally. The orbit is not well vascularized and the possibility of significant via-blood stream effects of retrobulbar injections is very remote In general, retrobulbar injections are given for the purpose of getting medications into the posterior segment of the globe and to affect the nerves and other structures in the retrobulbar space *Remington's Pharmaceutical Sciences*, 15th Ed , 1489–1504, (1975)

The following examples are intended to illustrate, but not to limit, the scope of the invention.

EXAMPLE I

Composition of Ophthalmic Solutions for Topical Administration to the Eye

	Composition at Concentration Indicated				
Ingredient	Vehicle	0 02%	0.1%	0 25%	0 5%
$NaH_2PO_4.H_2O$ 0.2 M	8 ml	8 ml	8 ml	8 ml	8 ml
$Na_2HPO_4.H_2O$ 42 ml 0 2 M	42 ml	42 ml	42 ml	42 ml	
Active Ingredient	0	0 02 g	0.1 g	0.25 g	0 5 g
NaCl	0 18 g	0 178 g	0 165 g	0 142 g	0 10 g

-continued

Ingredient	Composition at Concentration Indicated				
	Vehicle	0.02%	0.1%	0.25%	0.5%
Benzalkonium Chloride 50% w/w	0.02 g	0.02 g	0.02 g	0.02 g	0.02 g
Sterilized water q.s.	100 ml	100 ml	100 ml	100 ml	100 ml

The active ingredient in this example is 5-benzoyl-1,2-dihydro-3H-pyrrolo(1,2-a)pyrrole-1-carboxylic acid, but other compounds of this invention may be substituted therefor

The active compound of this example, in its trishydroxymethylaminomethane salt, was dissolved in buffered isotonic solutions containing benzalkonium chloride as a preservative. Volume was made up to 100 ml and pH adjusted to 7.4. The resulting solution was filtered through 0.45 microns millipore filter and were dispensed for use in dropper bottles

EXAMPLE 2

Eye Irritation Study

This example illustrates non-irritating properties of compounds of this invention when used as topical anti-inflammatories administered directly to the eye of an experimental animal.

To be effective topical anti-inflammatory agent, the compound must, first of all, itself prove to be non-irritating To determine the effects of various compounds on eye irritation, the comparative irritability test among known anti-inflammatories was designed wherein the irritation of the eye following the topical application of tested compound was measured and compared to the irritation of the eye following the application of other anti-inflammatory compound Each studied anti-inflammatory compound was tested individually on single animal by administering, at the same time, into one eye of the animal the ophthalmic solution with tested compound as an active ingredient and to the other eye vehicle ophthalmic solution only. An irritation caused by tested compounds, if any, was compared to non-irritating effect of vehicle ophthalmic solution applied to the other eye Irritation was measured by number of blinks of each eye during the exact period of time. Tests were performed on rats, dogs and monkeys

Protocol

Ophthalmic solutions with the 0.02%, 0.1% and 0.5% of 5-benzoyl-1,2-dihydro-3H-pyrrolo(1,2-a)pyrrole-1-carboxylic acid or Flurbiprofen as an active ingredient were prepared according to the procedure of Example 1. One drop of the tested ophthalmic solution with active ingredient was administered directly into the conjuctival sack of the rat's left eye At the same time one drop of vehicle was administered to the conjunctival sack of the rat's right eye. Irritation of each eye was measured by counting the number of blinks for one minute after the application. The results were expressed as the mean number of blinks±standard error per eye. The mean number of blinks/minute were averaged for the vehicle treatment and compared to the drug treated eye. Each compound was tested similarly in mongrel dogs and rhesus monkeys.

While Flurbiprofen has caused a severe eye irritation (it, for example, doubled number of blinks following the application of 0,5% solution) in rats, dogs and monkeys, the compounds of this invention did not illicite any irritation of the eyes in any of the three species at any concentration which was used for testing (i.e., 0,002–0.5%) and their effect was comparable to the effect of the vehicle ophthalmic solution without any drug added

EXAMPLE 3

Silver nitrate-induced neovascularization

This example illustrates topical anti-inflammatory effect of claimed compounds by testing their ability to inhibit neovascular growth induced by silver nitrate cauterization.

Corneal neovascularization is part of the normal inflammatory response to the keratitis—inflammation of the cornea. Corneal neovascularization follows corneal invasion by polymorphonuclear leukocytes The most serious consequence of neovascularization is the loss of corneal transparency combined with a biochemical modification of the corneal tissue that changes it from an avascular tissue not participating in the body's tissue immunity to one requiring a direct blood supply that partakes of antigen-antibody reactions Experimentally, neovascularization of the cornea may be induced by cauterization of the rat or rabbit cornea with silver nitrate *Amer. J. Pathol* 79, 537, 1975.

Protocol

Preliminary experiments have shown that rats elicited a more uniform response to a silver nitrate than rabbits Four groups of rats (12/group) were used for this study The center of the each rat's cornea was cauterized with silver nitrate applicator stick obtained from San Jose Surgical Supply. Treatment was started immediately after cauterization and comprised a topical administration of various concentrations of tested compounds of vehicle directly to the rat's eye

Vehicle ophthalmic solution and ophthalmic solution with 0.1%, 0.25% or 0.5% of 5-benzoyl-1,2-dihydro-3H-pyrrolo(1,2-a)pyrrole-1-carboxylic acid as an active ingredient were prepared according to the procedure of Example 1. Immediately after cauterization, one drop of tested ophthalmic solution was applied to the right eye and one drop of the vehicle was applied to the left eye four times each day always administering solutions containing tested compound or vehicle to the same eye as previously. Treatment was continued for 5 days

It has been found that cauterization caused a wide response and therefore the response to burning was graded to ensure that the mean response for each group was similar. The following scale was used to grade the response to burning

0	no burn visible
1+	cauterized area with no blister
2+	small blister
3+	moderate blister
4+	large blister

Because the burns which do not cause a blisters do not induce neovascularization, prior to a treatment initiation, rats were examined for the presence or absence of blisters and the rats who did not develop blisters were excluded from the study. Thus, the only rats with burns degree of 2+ to 4+ were used

The day after the last treatment, the degree of the neovascularization which developed around the cornea

was quantitated by determining the distance which the new blood vessels progressed toward the burn site. The following scale was used to determine the degree of the neovascularization:

0	blood vessels in cornea
1.5+	blood vessels ¼ distance to burn
2+	blood vessels ½ distance to burn
3+	blood vessels ¾ distance to burn
4+	blood vessels ¾ distance to burn
4.5	blood vessels ¾ distance to burn
6+	vessels reach burn

All evaluations were performed blindly, the investigator being unaware of which eye received tested compound and which received the vehicle At the completion of the study, the eyes were photographed using an OM-2 camera attached to a disecting microscope.

The data from these experiments show that the burn stimulus from group to group was reasonably uniform. While the lowest concentration (0.1%) of the tested compound did not cause statistically significant decrease in mean neovascularization; the solutions with 0.25% and 0.5% concentrations of tested compound inhibited significantly neovascularization caused by silver nitrate application.

EXAMPLE 4

Endotoxin Induced Uveitis

The uvea, the middle layer of the eye, consists of the choroid, the ciliary body and the iris Uveitis, inflammation of the uvea is characterized by change in the permeability of uvea vessels and by the leakage of inflammatory exudates into the aqueous. Uveitis may be experimentally induced by intravenous administration of endotoxin (Nature, 286 611, 1980) A model was developed in rabbits in which the uveitis, induced experimentally by endotoxin, is monitored by fluorophotometry. This experiment illustrates the utility of compounds of current invention in reducing the degree of vascular permeability developed during uveitis.

Protocol

New Zealand white rabbits were anesthetized with ketamine (35 mg/kg, i m.) and xylazine (5 mg/kg, i m) dextran-isothiocyanate-fluorescein (FITC) (m.w.=64,200, 100 mg/kg as a 10% solution) was injected into their marginal ear vein. 15 minutes later, a dose of 2 5 μg/kg of endotoxin (lipopolysaccharide) isolated from Salmonella typhimurium was injected into the same marginal vein. The rabbit was placed in front of fluorophotometer and a blue light was focused into the eye. The resulting fluorescence, emitted by dextran-FITC, was detected by a photomultiplier tube. Scans were made of the right and left eyes of each rabbit after dextran-FITC administration, and 90 minutes after endotoxin administration

The dextran-FITC concentration in the aqueous humor was determined using a fluorophotometer manufactured by Coherent Medical Division, Palo Alto, Calif This devise consist of a scanning optic head controlled by a Commodore Pet Computer, which runs the scan, stores, and processes obtained data.

Initially, most of the dextran-FITC was present in the retinal vessels but after period of 60 minutes, considerable amount of dextran-FITC appeared in the aqueous, indicating an alteration in the vascular permeability of the vessels in the iris and ciliary body caused by endotoxin.

To test a compound, one drop of 0.5% ophthalmic solution with the tested compound as an active ingredient was applied to the right eye of the rabbit two hours prior to endotoxin injection, one hour prior to endotoxin injection, at the time of endotoxin injection, thirty minutes and sixty minutes after the endotoxin challenge. At the same times, the left eye of the rabbit received the vehicle ophthalmic solution only. The effectivity of the compound was measured by following a progressive increase in dextran-FITC leakage into the aqueous of both eyes.

The results of this study indicate that the eye pre- and post-treated with compounds of this invention were protected effectively against endotoxin-induced leakage of dextran-FITC into aqueous Vascular permeability in treated eye was approximately ten times lower, with degree of significance smaller than 0.01 when compared with non-treated eye.

EXAMPLE 5

Effect on Increased Intraoccular Pressure

This example illustrates the effect of compounds of current invention on intraoccular pressure. Arachidonic acid, a prostaglandin substrate, when topically applied to the eye increases intraoccular pressure similarly to that observed in glaucoma.

Protocol

Female Dutch belted rabbits (Nitabell Rabbitry, Hayward, Calif.) weighing 1 5-2.0 kg were anesthetized with topical anesthetics (0.5% proparacaine HCl) obtained from Squibb Prior to the beginning of the experiments, normal intraoccular pressure in both eyes of the rabbits were established using McKay-Marg Electronic Tonometer. Obtained results were expressed in mm of mercury. By this preliminary study it was determined that there were no significant differences in intraoccular pressure readings between the right and left eyes of normal rabbits

The actual testing studies were divided into two substudies with the purpose for the first one to determine whether the topical application of tested compound will increase intraoccular pressure, and with the purpose of the second one to determine whether, when applied to the eye with already increased intraoccular pressure, it will be able to decrease said pressure significantly.

First Study

After the initial intraoccular pressure of each animal was determined, ophthalmic solution with 0 5% of tested compound was applied to the rabbit left eye and the vehicle ophthalmic solution was applied to the rabbit right eye. Two hours later, the pressures of both eyes were recorded, and the data were analyzed using a paired "t" test

Neither the vehicle ophthalmic solution, nor the ophthalmic solution with 0,5% of an active ingredient increased intraoccular pressure in the two hours interval after the administration Both measured pressures were exactly the same as those established by preliminary experiment Thus, the tested compounds did not show any direct effect on normal intraoccular pressure.

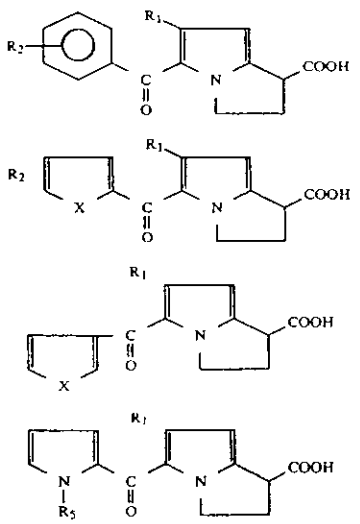
Second Study

In the second study, the initial base-line of intraocular pressure was again established for each animal. This was followed by application of one drop of 0.5% of the ophthalmic solution containing the tested compound as active ingredient into rabbit's left eye and the vehicle ophthalmic solution to the rabbit's right eye at the time zero and 15 minutes later. Thirty minutes from the first application of tested solutions one drop of a 2% solution of arachidonic acid dissolved in peanut oil was applied to both eyes. Forty-five minutes from the time zero intraocular pressures of both eyes were measured and the data were analyzed using a paired "t" test.

As expected, arachidonic acid increased intraocular pressure in the right eyes of the animals but not in the left eye which was pretreated with tested drug. Ophthalmic solution with 0.5% of the tested compound applied twice prior to arachidonic acid was able to prevent this increase in intraocular pressure. The same solution applied only once did not significantly affect intraocular pressure.

What is claimed

1. A method for treating inflammation of the eye in mammals which method comprises topical application to the eye of a mammal in need thereof a therapeutically effective amount of a pharmaceutical ophthalmic composition containing 0.005-1% wt/vol of a compound chosen from those represented by the formulas:



and the individual (l-) and (d-)acid isomers thereof and the pharmaceutically acceptable non-toxic esters and salts thereof, wherein

R_1 represents hydrogen; lower alkyl group having from one to four carbon atoms; chloro or bromo,

R_2 represents hydrogen, a lower alkyl group having from one to four carbon atoms, a lower alkoxy group having from one to four carbon atoms, chloro, bromo, fluoro; or $R_4S(O)n$ wherein

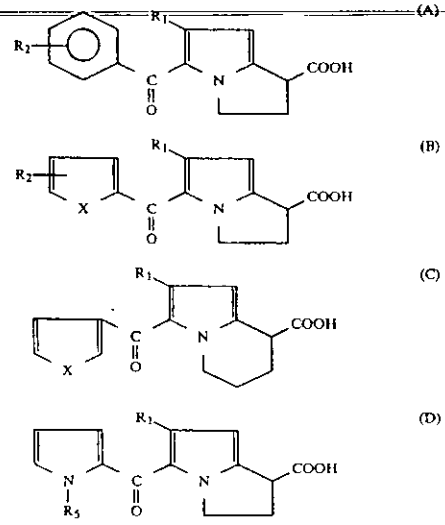
R_4 is lower alkyl and

n is the integer 0, 1 or 2;

X represents oxygen or sulphur; and

R_5 represents hydrogen or lower alkyl group having from one to four carbon atoms

2. A method for treating corneal neovascularization, uveitis and cystoid macular edema in mammals which method comprises topical application to the eye of a mammal in need thereof a therapeutically effective amount of a pharmaceutical ophthalmic composition containing 0.005-1% wt/vol of a compound chosen from those represented by the formulas·



and the individual (l-) and (d)acid isomers thereof and the pharmaceutically acceptable non-toxic esters and salts thereof, wherein

R_1 represents hydrogen; lower alkyl group having from one to four carbon atoms; chloro or bromo;

R_2 represents hydrogen, a lower alkyl group having from one to four carbon atoms, a lower alkoxy group having from one to four carbon atoms, chloro, bromo, fluoro, or $R_4S(O)n$ wherein

R_4 is lower alkyl and

n is the integer 0, 1 or 2,

X represents oxygen or sulphur; and

R_5 represents hydrogen or lower alkyl group having from one to four carbon atoms.

3. The method of claim 2 for treating corneal neovascularization.

4. The method of claim 2 for treating uveitis.

5 The method of claim 2 for treating cystoid macular edema.

6 The method of claim 2 wherein compounds are represented by those of Formula (A).

7. The method of claim 6 wherein R_1 is hydrogen

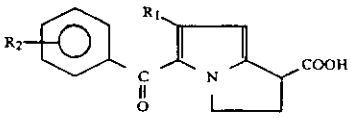
8 The method of claim 6 wherein R_2 is hydrogen, namely 5-benzoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylic acid

9 The method of claim 6 wherein R_2 is R_4S where R_4 is methyl and the R_2 substituent is at the para-position of the phenyl ring, namely 5-(p-methylthio)benzoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylic acid

10 The method of claim 6 wherein R_2 is methoxy at the para-position, namely 5-(p-methoxy)-benzoyl-1,2-dihydro-3H-pyrrolo-[1,2-a]pyrrole-1-carboxylic acid.

11. The method of claim 6 wherein R_1 is methyl.

12. A topical ophthalmic pharmaceutical composition for the treatment of inflammation of the eye comprising an 99% to 99.995% wt/vol of ophthalmologically acceptable excipient in admixture with 0.005–1% wt/vol of a compound chosen from those represented by the formulas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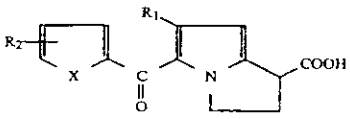
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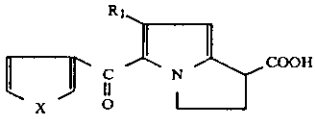
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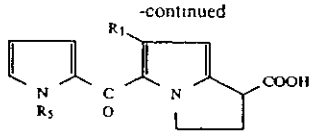
(D)

and the individual (l-) and (d-)acid isomers thereof and the pharmaceutically acceptable non-toxic esters and salts thereof, wherein

R_1 represents hydrogen, lower alkyl group having from one to four carbon atoms, chloro or bromo;

R_2 represents hydrogen, a lower alkyl group having from one to four carbon atoms, a lower alkoxy group having from one to four carbon atoms, chloro, bromo, fluoro; or $R_4S(O)n$ wherein

R_4 is lower alkyl and

n is the integer 0, 1 or 2,

X represents oxygen or sulphur; and

R_5 represents hydrogen or lower alkyl group having from one to four carbon atoms.

13 The topical pharmaceutical ophthalmic composition of claim 11 wherein the compound is represented by formula (A)

14. The topical pharmaceutical ophthalmic composition of claim 13 wherein R_1 is hydrogen.

15. The topical pharmaceutical ophthalmic composition of claim 14 wherein R_2 is hydrogen; namely, 5-benzoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylic acid.

16. The topical pharmaceutical ophthalmic composition of claim 14 wherein R_2 is R_4S where R_4 is methyl and the R_2 substituent is at the para-position of the phenyl ring, namely, 5-(p-methylthio)benzoyl-1,2-dihydro-3H-pyrrolo-[1,2-a]-pyrrole-1-carboxylic acid.

17. The topical pharmaceutical ophthalmic composition of claim 14 wherein R_4 is methoxy at the para-position; namely, 5-(p-methoxy)-benzoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylic acid.

18. The topical pharmaceutical ophthalmic composition of claim 12 wherein the compound is chosen from those represented by formula (A) wherein R_1 is methyl.

* * * * *

US005110493A

United States Patent [19]

Cherng-Chyi et al.

[11] Patent Number: 5,110,493

[45] Date of Patent: May 5, 1992

[54] **OPHTHALMIC NSAID FORMULATIONS CONTAINING A QUATERNARY AMMONIUM PRESERVATIVE AND A NONIONIC SURFACTANT**

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[21] Appl. No.: **624,027**

[22] Filed: **Dec. 7, 1990**

Related U.S. Application Data

[63] Continuation of Ser. No 96,173, Sep 11, 1987, abandoned

[51] **Int. Cl.**[5] **A61K 31/40**

[52] **U.S. Cl.** **514/413**; 252/106, 514/912, 514/914

[58] **Field of Search** 514/413, 912, 914, 252/106

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Primary Examiner—A. Lionel Clingman
Assistant Examiner—Mary C DiNunzio
Attorney, Agent, or Firm—Derek P. Freyberg, Karl Bozicevic

[57] **ABSTRACT**

Stable, clear, antimicrobially effective, ophthalmic formulations include an ophthalmologically effective amount of a drug, especially a —COOH group-containing drug or a NSAID, and a preservative system formed of a quaternary ammonium preservative and a nonionic surfactant, all in an aqueous vehicle. These formulations are useful for treating diseases that are either caused by, associated with or accompanied by inflammatory processes, including, among others, glaucoma, cystoid macular edema, uveitis, diabetic retinopathy and conjunctivitis, or any trauma caused by eye surgery or eye injury.

16 Claims, No Drawings

OPHTHALMIC NSAID FORMULATIONS CONTAINING A QUATERNARY AMMONIUM PRESERVATIVE AND A NONIONIC SURFACTANT

CROSS-REFERENCE TO RELATED APPLICATION

This application is a continuation of our copending application Ser. No. 07/096,173, filed Sep 11, 1987 now abandoned.

BACKGROUND OF THE INVENTION

The present invention relates to improved ophthalmic formulations, particularly to ophthalmic formulations for anti-inflammatory drugs, and specifically to an improved preservative system for ophthalmic formulations of carboxyl ("—COOH") group-containing drugs, especially non-steroidal anti-inflammatory drugs ("NSAIDs").

The invention also relates to methods of using these formulations for treating diseases that are either caused by, associated with or accompanied by inflammatory processes, including, among others, glaucoma, cystoid macular edema, uveitis, diabetic retinopathy and conjunctivitis, or any trauma caused by eye surgery or eye injury

The topical use of NSAIDs, particularly pyrrolo pyrroles, in the treatment of ophthalmic diseases was first taught in U.S Pat. No 4,454,151, where NSAID compounds (such as those described in U.S Pat Nos 4,089,969, 4,232,038, 4,087,539 and 4,097,579) were exemplified in formulation with $NaH_2PO_4 H_2O$, $Na_2HPO_4 H_2O$, NaCl, benzalkonium chloride ("BAC") and sterilized water While the formulations described in the '151 patent were efficacious, a complex was found to form between the NSAID and the BAC. The formulations did not, therefore, have the stability desired for shelf life in commercial applications A reasonable minimum shelf life is at least about one year, representing sufficient time to package, ship, and store a formulation without having to replace expired stock too frequently. Thus, the present invention entails an improvement over the formulations described in the '151 patent

In general, an ophthalmic formulation contains an active compound and various ophthalmologically acceptable excipients, in the form of a solution, an ointment, a suspension, etc. An excipient is ophthalmologically acceptable if it is non-irritating to the eye and if its active ingredient penetrates the blood-aqueous barrier and/or difuses through the various ocular substructures to the site where it is pharmacologically active. The excipients can include a tonicifier, a preservative, a surfactant, a buffering system, a chelating agent, a viscosity agent as well as other stabilizing agents. Ophthalmic formulations must be sterile, and if intended for multiple dosing regimens, must be preserved with an effective anti-microbial agent.

Organo-mercurials (e g., thimerosal, phenylmercuric acetate and phenylmercuric nitrate) have been used extensively as the preservative in ophthalmic solutions. These compounds, however, pose difficulties due to potential mercury toxicity as well as poor chemical stability. Benzalkonium chloride, a quaternary ammonium compound, has been widely used in ophthalmic solutions, and is considered to be the preservative of choice However, BAC has typically been considered

to be incompatible with anionic drugs (e g , salicylates or nitrates, etc) and can be inactivated by surfactants.

Many NSAIDs (such as ketorolac, indomethacin, flurbiprofen and suprofen) are being developed for ocular use because of their activity as anti-inflammatory agents as well as their ability to prevent cystoid macular edema.

These NSAIDs have proven to be incompatible with quaternary ammonium compounds such as BAC because they can form a complex with them, rendering the preservative less available to serve its function, as is the case with other ophthalmic drugs that contain a —COOH group. Thus, less preferred preservatives have been used in such ophthalmic formulations. For example, Ocufen Ophthalmic solution, the first NSAID (flurbiprofen) approved by the FDA for ophthalmic use, incorporates thimerosal (with EDTA) as its preservative system.

It has remained desired to provide a stable, clear, antimicrobially effective ophthalmic formulation for NSAIDs using BAC as the preservative, and an improved preservative system for —COOH group containing ophthalmic drugs.

SUMMARY OF THE INVENTION

It has now been discovered that stable, i.e., clear and antimicrobially effective, NSAID-containing ophthalmic formulations can be prepared that do not include an organo-mercurial preservative.

In one aspect of the invention, these compositions include an ophthalmologically effective amount of a NSAID, a quaternary ammonium preservative and a stabilizing amount of a nonionic surfactant, all in an aqueous vehicle.

Another aspect is an antimicrobially effective preservative system for ophthalmic drugs having a —COOH group, including a quaternary ammonium preservative and a stabilizing amount of a nonionic surfactant.

In a third aspect of the invention, methods for treating ophthalmic diseases in mammals using the ophthalmic pharmaceutical formulations of the invention are also disclosed These diseases are those that are either caused by, associated with or accompanied by inflammatory processes, including, among others, glaucoma, cystoid macular edema, uveitis, diabetic retinopathy and conjunctivitis, or any trauma caused by eye surgery or eye injury.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

DEFINITIONS

As used herein, the term "NSAID" means an ophthalmologically acceptable non-steroidal anti-inflammatory drug.

As used herein, the term "q s." means adding a quantity sufficient to achieve a stated function, e.g., to bring a solution to the desired volume (i.e., 100%).

As used herein, the term "treatment" or "treating" means any treatment of a disease in a mammal, including:

(i) preventing the disease, that is, causing the clinical symptoms of the disease not to develop,

(ii) inhibiting the disease, that is, arresting the development of clinical symptoms; and/or

(iii) relieving the disease, that is, causing the regression of clinical symptoms

As used herein, the term "effective amount" means a dosage sufficient to provide treatment for the disease state being treated. This will vary depending on the patient, the disease and the treatment being effected.

As used herein, the term "antimicrobially effective" means ability to withstand the U S. Pharmacopia antimicrobial challenge.

As used herein, the term "stabilizing" means keeping a formulation clear and antimicrobially effective for its minimum reasonable shelf life, e g , at least one year.

FORMULATIONS

The formulations of the present invention include a NSAID active agent in an effective amount for ophthalmic treatment, a quaternary ammonium preservative, a stabilizing amount of a nonionic surfactant, optionally including other excipients such as a chelating agent, a tonicifier, a buffering system, a viscosity agent as well as other stabilizing agents. Ophthalmic solutions and suspensions typically contain an aqueous vehicle rather than an oily vehicle. Ophthalmic formulations must be sterile, and if intended for multiple dosing regimens, must be antimicrobially effective for their minimum reasonable shelf life, e.g., at least one year, and preferably two to three years or more The ingredients used in the formulations of the present invention are typically commercially available or can be made by methods readily known to those skilled in the art.

Pharmaceutical ophthalmic formulations typically contain an effective amount, e.g., 0.001% to 10% wt/vol, most preferably 0.005% to 1% of an active ingredient (e.g., the NSAID of the present invention). The amount of active ingredient will vary with the particular formulation and the disease state for which it is intended The total concentration of solutes should be such that, if possible, the resulting solution is isotonic with the lacrimal fluid (though this is not absolutely necessary) and has a pH in the range of 6–8.

The formulations of the present invention are prepared as solutions incorporating the above-described ingredients within the following approximate ranges

Ingredient	Amount
Active Agent	0 001% to 10 0% wt/vol.
Preservative	0 001% to 1 0% wt/vol
Surfactant	0 001% to 1 0% wt/vol.
Other Excipients	0% to 10 0% wt/vol; and
Purified Water	q s to 100%

Optional other excipients, such as a chelating agent and a tonicifier, are used in the following approximate proportions:

Ingredient	Amount
Chelating agent	0 01% to 1 0% wt/vol;
Tonicifier	q s. to achieve isotonicity with lacrimal fluid, and
1N NaOH or 1N HCl	q s to adjust pH to 6 0 to 8 0

In a preferred ophthalmic NSAID solution, the ingredients are combined in the following proportions:

Ingredient	Amount
NSAID	0.50% wt/vol.,

-continued

Ingredient	Amount
BAC (50% aq soln)	0 02% wt/vol;
Octoxynol 40 (70% aq soln)	0 01% wt/vol
EDTA Na2	0 10% wt/vol;
NaCl	q s for isotonicity with lacrimal fluid.
1N NaOH or 1N HCl	q s to adjust pH to 7 4 ± 0 4, and
Purified Water	q s. to 100%.

The invention relates primarily to formulations having as the active agent ophthalmologically acceptable drugs (including the esters and pharmaceutically acceptable salts thereof) that can form a complex with a quaternary ammonium compound, particularly NSAIDs and drugs with a carboxyl group.

NSAIDs useful in the practice of this invention include, for example, ketorolac (and the other compounds described as being ophthalmologically effective in U.S. Pat. No. 4,454,151 to Waterbury, issued Jun. 12, 1984, the pertinent portions of which are incorporated herein by reference), indomethacin, flurbiprofen sodium, and suprofen, including the esters and pharmaceutically acceptable salts thereof

Preservatives useful in the formulations of the present invention include quaternary ammonium compounds, such as cetyltrimethylammonium bromide, cetylpyridinium chloride and preferably, benzalkonium chloride.

The nonionic surfactants useful in the formulations of the present invention are preferably polyoxyethylated surfactants including polyoxyethylene hydrogenated vegetable oils, such as polyethylene 60 hydrogenated castor oil, manufactured and sold by Kao Corp. of Japan under the trade name Emanon CH-60, and preferably ethoxylated octylphenol compounds, such as Octoxynol 10 and most preferably Octoxynol 40, manufactured and sold by GAF under the trade name Igepal CA897 (a 70% aqueous solution of Octoxynol 40).

Among the optional excipients, the chelating agents useful in the formulations of the present invention include 8-hydroxyquinoline sulfate, citric acid, and preferably disodium edetate. Under certain conditions, the chelating agent may also enhance the anti-microbial effect due to its ability to render essential metal ions unavailable to the microbes

Buffering systems optionally useful in the formulations of the present invention are based on, for example, citrate, borate, or phosphate.

Tonicifiers optionally useful in the formulations of the present invention include dextrose, potassium chloride and/or sodium chloride, preferably sodium chloride.

Viscosity agents optionally useful in the formulations of the present invention include the cellulose derivatives such as hydroxypropylmethyl cellulose, sodium carboxymethylcellulose, and hydroxyethylcellulose.

Other optional excipients useful in the formulations of the present invention include stabilizing agents such as antioxidants, e.g., sodium metabisulfate and ascorbic acid, depending on the NSAID used.

These formulations are prepared by dissolving the solutes (e.g., the NSAID, the preservative, the surfactant, the chelating agent, and the buffering agent) in a suitable quantity of water, adjusting the pH to about 6–8, preferably 6.8–8 0 and most preferably 7.4, making

a final volume adjustment to 100% with additional water, and sterilizing the preparation using any suitable method known to those in the art

It has been discovered that ophthalmic formulations incorporating the preservative system of the invention are physically stable (i.e., remain clear) and functionally stable (i.e., remain antimicrobially effective) for at least the minimum reasonable shelf life of such products.

PREFERRED FORMULATIONS

The preferred preservative system of the invention includes a quaternary ammonium preservative and a stabilizing amount of a nonionic surfactant.

The preferred ophthalmic formulation of the invention includes a NSAID active agent in an effective amount for ophthalmic treatment and an antimicrobially effective amount of the above-described preferred preservative system

The preferred preservative of the invention is benzalkonium chloride.

The preferred surfactant of the invention is Octoxynol 40, especially when combined with benzalkonium chloride.

The preferred chelating agent of the invention is disodium edetate, especially when combined with benzalkonium chloride and Octoxynol 40.

The preferred ophthalmic solutions of the invention include a NSAID, benzalkonium chloride, Octoxynol 40 and disodium edetate.

A preferred ophthalmic NSAID solution has the following formulation:

Ingredient	Amount
NSAID	0.50% wt/vol
BAC (50% aq soln)	0.02% wt/vol
Octoxynol 40 (70% aq soln)	0.01% wt/vol
EDTA Na_2	0.10% wt/vol
NaCl	q.s. for isotonicity with lacrimal fluid
1N NaOH or 1N HCl	q.s. to adjust pH to 7.4 ± 0.4
Purified Water	q.s. to 100%

Most preferred is the ophthalmic solution according to the above formulation wherein the NSAID is Ketorolac Tromethamine

UTILITY AND ADMINISTRATION

This invention is directed to NSAID ophthalmic formulations and a method useful for treating ophthalmic diseases in mammals. These diseases are either caused by, associated with or accompanied by inflammatory processes, including, among others, glaucoma, cystoid macular edema, uveitis, diabetic retinopathy and conjunctivitis, or any trauma caused by eye surgery or eye injury.

The method of this invention is both curative and preventative. Where applied, for example, pre-surgically or immediately post-traumatically, i.e. before inflammation develops, it prevents development of inflammation. When applied directly to the eye suffering from any of the named opthalmic diseases, it supresses already developed inflammatory processes.

Opthalmic formulations are typically administered by topical application to the eyelids or for instillation into the space (cul-de-sac) between the eyeball and the eyelids, by topically applied ophthalmic solutions, suspensions or ointments, or by subconjunctival injection

The dosage level will, of course, depend on the concentration of the drops, the condition of the subject and the individual magnitude of responses to treatment. However, typical dosage ranges might be about 2–10 drops of 0.1% solution of active ingredient per day.

For a more detailed discussion of ophthalmic formulations, their preparation and administration, see *Remington's Pharmaceutical Sciences*, 15th Ed., pages 1489–1504, (1975).

TESTING

Ophthalmic formulations such as the solutions of the present invention are typically tested for physical stability, chemical stability, and preservative efficacy, both when they are first manufactured and after a fixed period of time (e.g., after two years) They are generally considered to be safe and clinically acceptable if proven to be well tolerated in the eye.

Physical stability is determined by observation of a solution after expiration of a fixed period of time. A solution is considered to be physically stable if its appearance (e.g., color and clarity) does not change and if the pH remains constant, within acceptable limits. Chemical stability involves a routine chemical analysis of the solution, to be sure that its active ingredient and the excipients have not changed after a fixed period of time.

Preservative efficacy is tested by the procedure described in the U.S. Pharmacopia Compendiary, whereby a solution is challenged with a microbe and a determination is made as to whether the microbe survives in it.

EXAMPLES

The following examples are given to enable those skilled in the art to more clearly understand and to practice the present invention They should not be considered as a limitation on the scope of the invention, but merely as being illustrative and representative thereof.

EXAMPLE 1

This example illustrates the preparation of a representative pharmaceutical formulation for ophthalmic administration containing the NSAID Ketorolac Tromethamine.

Ingredient	Amount
Ketorolac Tromethamine	0.50% wt/vol
BAC (50% aq soln)	0.02% wt/vol
Octoxynol 40 (70% aq soln)	0.01% wt/vol.
EDTA Na_2	0.10% wt/vol.
NaCl	0.79% wt/vol.

The above ingredients are mixed, adding purified water until they are dissolved, the pH is adjusted to 7.4±0.4 and the balance of the formulation is made up with purified water, adding a quantity sufficient to make 100% volume. The solution is then sterilized.

Other NSAIDs, such as those described above, can be used as the active compound in the preparation of the formulation of this example.

EXAMPLE 2

This example illustrates the preparation of a representative pharmaceutical formulation for ophthalmic administration containing the NSAID Ketorolac Tromethamine

Ingredient	Amount
Ketorolac Tromethamine	0.50% wt/vol
BAC (50% aq soln.)	0.01% wt/vol
Octoxynol 40 (70% aq soln.)	0.02% wt/vol
EDTA Na_2	0.20% wt/vol
NaCl	0.79% wt/vol

The above ingredients are mixed, adding purified water until they are dissolved, the pH is adjusted to 7.4±0.4 and the balance of the formulation is made up with purified water, adding a quantity sufficient to make 100% volume. The solution is then sterilized.

Other NSAIDs, such as those described above, can be used as the active compound in the preparation of the formulation of this example.

EXAMPLE 3

This example illustrates the preparation of a representative pharmaceutical formulation for ophthalmic administration containing the NSAID Ketorolac Tromethamine.

Ingredient	Amount
Ketorolac Tromethamine	0.10% wt/vol
BAC (50% aq soln.)	0.004% wt/vol
Octoxynol 40 (70% aq soln.)	0.004% wt/vol
EDTA Na_2	0.05% wt/vol
NaCl	0.88% wt/vol

The above ingredients are mixed, adding purified water until they are dissolved, the pH is adjusted to 7.4±0.4 and the balance of the formulation is made up with purified water, adding a quantity sufficient to make 100% volume. The solution is then sterilized.

Other NSAIDs, such as those described above, can be used as the active compound in the preparation of the formulation of this example.

EXAMPLE 4

This example illustrates the preparation of a representative pharmaceutical formulation for ophthalmic administration containing the NSAID flurbiprofen sodium.

Ingredient	Amount
Flurbiprofen Sodium	0.03% wt/vol
BAC (50% aq soln.)	0.02% wt/vol
Octoxynol 40 (70% aq soln.)	0.01% wt/vol
EDTA Na_2	0.10% wt/vol
NaCl	0.90% wt/vol

The above ingredients are mixed, adding purified water until they are dissolved, the pH is adjusted to 7.4±0.4 and the balance of the formulation is made up with purified water, adding a quantity sufficient to make 100% volume. The solution is then sterilized.

Other ophthalmic drugs and NSAIDs, such as those described above, can be used as the active compound in the preparation of the formulation of this example.

EXAMPLE 5

Physical stability of the formulations of the present invention is measured by preparing clear formulations, e.g., according to the foregoing Examples, sealing them in sterilized containers, and observing the clarity of the solution after a period of one month and again after five months. Solutions that remain clear are considered stable in this procedure.

The formulations of the present invention have proven to be stable when tested in accordance with the above procedure. Formulations using surfactants other than the nonionic surfactants of the invention did not remain clear and were not stable

EXAMPLE 6

Preservative efficacy of the formulations of the present invention is measured by preparing formulations, e.g., according to the foregoing Examples, and subjecting them to the U.S. Pharmacopia antimicrobial challenge.

The formulations of the present invention demonstrate preservative efficacy when tested in accordance with the above procedure.

While the present invention has been described with reference to the specific embodiments thereof, it should be understood by those skilled in the art that various changes may be made and equivalents may be substituted without departing from the true spirit and scope of the invention. In addition, many modifications may be made to adapt a particular situation, material, composition of matter, process, process step or steps, to the objective, spirit and scope of the present invention. All such modifications are intended to be within the scope of the claims appended hereto

What is claimed is:

1. An ophthalmologically acceptable non-steroidal anti-inflammatory drug formulation, comprising:

an ophthalmologically acceptable non-steroidal anti-inflammatory carboxyl group-containing drug in an effective amount for ophthalmic treatment between 0.001% and 10.0% wt/vol;

a quaternary ammonium preservative in an antimicrobially effective amount between 0.001% and 1.0% wt/vol;

an ethoxylated alkyl phenol that conforms generally to the formula $C_8H_{17}C_6H_4(OCH_2CH_2)_nOH$ where n has an average value of 40 in a stabilizing amount between 0.001% and 1.0% wt/vol; and an aqueous vehicle q.s. to 100%

2. The ophthalmologically acceptable non-steroidal anti-inflammatory drug formulation of claim 1 wherein said quaternary ammonium preservative is benzalkonium chloride

3. The ophthalmologically acceptable non-steroidal anti-inflammatory drug formulation of claim 2 wherein said ophthalmologically acceptable non-steroidal anti-inflammatory carboxyl group-containing drug is selected from the group selected from ketorolac, indomethacin, flurbiprofen, and suprofen.

4. The ophthalmologically acceptable non-steroidal anti-inflammatory drug formulation of claim 3 wherein said ophthalmologically acceptable non-steroidal anti-

inflammatory carboxyl group-containing drug is ketorolac tromethamine

5 The ophthalmologically acceptable non-steroidal anti-inflammatory drug formulation of claim 1, further comprising

a chelating agent in an amount between 0.01% and 1.0% wt/vol;

a tonicifier q.s. to achieve isotonicity with lacrimal fluid; and

1N NaOH or 1N HCl q.s. to adjust pH to 7.4±0.4

6 The ophthalmologically acceptable non-steroidal anti-inflammatory drug formulation of claim 1 comprising:

ophthalmologically acceptable non-steroidal anti-inflammatory carboxyl group-containing drug	0.50% wt/vol.
BAC (50% aq. soln.)	0.02% wt/vol.
an ethoxylated alkyl phenol that conforms generally to the formula $C_8H_{17}C_6H_4(OCH_2CH_2)_nOH$ where n has an average value of 40 (70% aq. soln.)	0.01% wt/vol.
Na_2EDTA	0.10% wt/vol.
NaCl	q.s. for isotonicity with lacrimal fluid
1N NaOH or 1N HCl	q.s. to pH 7.4 ± 0.4, and
purified water	q.s. to 100%

7 The ophthalmologically acceptable non-steroidal anti-inflammatory drug formulation of claim 6 comprising

ketorolac tromethamine	0.50% wt/vol
BAC (50% aq. soln.)	0.02% wt/vol.
an ethoxylated alkyl phenol that conforms generally to the formula $C_8H_{17}C_6H_4(OCH_2CH_2)_nOH$ where n has an average value of 40 (70% aq. soln.)	0.01% wt/vol
Na_2EDTA	0.10% wt/vol
NaCl	0.79% wt/vol.
1N NaOH or 1N HCl	q.s. to pH 7.4 ± 0.4 and
purified water	q.s. to 100%

8 A method of treating an ophthalmic disease caused by, associated with, or accompanied by inflammatory processes, comprising administering to a mammal suffering therefrom a formulation comprising:

an ophthalmologically acceptable non-steroidal anti-inflammatory carboxyl group-containing drug in an effective amount for ophthalmic treatment between 0.001% and 10.0% wt/vol;

a quaternary ammonium preservative in an antimicrobially effective amount between 0.001% and 1.0% wt/vol;

an ethoxylated alkyl phenol that conforms generally to the formula: $C_8H_{17}C_6H_4(OCH_2CH_2)_nOH$ where n has an average value of 40 in a stabilizing amount between 0.001% and 1.0% wt/vol, and an aqueous vehicle q.s. to 100%.

9. The method of claim 8, wherein said quaternary ammonium preservative is benzalkonium chloride.

10 The method of claim 9 wherein said ophthalmologically acceptable non-steroidal anti-inflammatory carboxyl group-containing drug is selected from the group selected from ketorolac, indomethacin, flurbiprofen, and suprofen.

11 The method of claim 10 wherein said ophthalmologically acceptable non-steroidal anti-inflammatory carboxyl group-containing drug is ketorolac tromethamine

12. The method of claim 8 wherein the formulation further comprises.

a chelating agent in an amount between 0.01% and 1.0% wt/vol;

a tonicifier q.s. to achieve isotonicity with lacrimal fluid; and

1N NaOH or 1N HCl q.s. to adjust pH to 7.4±0.4.

13. The method of claim 8 wherein the formulation comprises:

ophthalmologically acceptable non-steroidal anti-inflammatory carboxyl group-containing drug	0.50% wt/vol.
BAC (50% aq. soln.)	0.02% wt/vol.
an ethoxylated alkyl phenyl that conforms generally to the formula $C_8H_{17}C_6H_4(OCH_2CH_2)_nOH$ where n has an average value of 40 (70% aq. soln.)	0.01% wt/vol
Na_2EDTA	0.10% wt/vol
NaCl	q.s. for isotonicity with lacrimal fluid
1N NaOH or 1N HCl	q.s to pH 7.4 ± 0.4 and
purified water	q.s. to 100%

14 The method of claim 13 wherein the formulation comprises

ketorolac tromethamine	0.50% wt/vol.
BAC (50% aq. soln.)	0.02% wt/vol.
an ethoxylated alkyl phenol that conforms generally to the formula $C_8H_{17}C_6H_4(OCH_2CH_2)_nOH$ where n has an average value of 40 (70% aq. soln.)	0.01% wt/vol
Na_2EDTA	0.10% wt/vol.
NaCl	0.79% wt/vol.
1N NaOH or 1N HCl	q.s. to pH 7.4 ± 0.4 and
purified water	q.s. to 100%

15. An antimicrobially effective preservative system for an ophthalmologically acceptable non-steroidal anti-inflammatory carboxyl group-containing drug formulation, comprising:

a quaternary ammonium preservative in an antimicrobially effective amount between 0.001% and 1.0% wt/vol of the formulation; and

an ethoxylated alkyl phenol that conforms generally to the formula: $C_8H_{17}C_6H_4(OCH_2CH_2)_nOH$ where n has an average value of 40 in a stabilizing amount between 0.001% and 1.0% wt/vol of the formulation.

16 The preservative system of claim 15 wherein said preservative is benzalkonium chloride.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 5,110,493
DATED : May 5, 1992
INVENTOR(S) : Cherng-Chyi Roger Fu and Deborah M. Lidgate

It is certified that error appears in the above-indentified patent and that said Letters Patent is hereby corrected as shown below:

On the title page, under item [19], delete "Cherng-Chyi" and insert therefor --Fu --.

Item [75] Inventors: delete "Roger F. Cherng-Chyi", and insert therefor --Cherng-Chyi R. Fu --.

Signed and Sealed this

Twenty-fourth Day of August, 1993

Attest:

BRUCE LEHMAN

Attesting Officer

Commissioner of Patents and Trademarks

[redacted]

ALLERGAN, INC.

DEBARMENT CERTIFICATION

Reference: NDA 21-528
Ketorolac Tromethamine Ophthalmic Solution 0.4%

Under the provisions of Section 306(k) of the Federal Food, Drug and Cosmetic Act, Allergan has made a diligent effort to insure that no individual, corporation, partnership or association debarred under Section 306(a) or 306(b) of the Act, as referenced above, has provided any services in connection with this application.

Allergan, Inc. further certifies that it did not and will not use in any capacity, the services of any individual, corporation, partnership or association debarred under Section 306(a) or 306(b) of the Federal Food, Drug and Cosmetic Act in connection with this application.

Peter Krezel
Senior Vice President
Global Regulatory Affairs

July 9, 2002
Date

LIST OF PRINCIPAL INVESTIGATORS/SUBINVESTIGATORS – 191578-002

Inv. ID No.	Principal Investigator	Subinvestigators	Address
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3751	Eric Donnenfeld, MD		Ophthalmic Consultants of Long Island 2000 North Village Avenue, Suite 402 Rockville Center, NY 11570 Island Eye Surgicenter 255 Glen Cove Road Carle Place, NY 11514 TLC Laser Eye Centers 200 Garden City Plaza, Suite 130 Garden City, NY 11530
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2947	Robert Snyder, MD*		University of Arizona Department of Ophthalmology 707 N Alvernon Way Third Floor, Suite 301 Tucson, AZ 85711
2298	Richard Yee, MD		Herman Eye Center, Jones Pavilion 6411 Fannin, 7th Floor Houston, TX 77030

*Included for completeness; these investiga[illegible] subinvestigators have Forms FDA 3455 attached.

LIST OF PRINCIPAL INVESTIGATORS/SUBINVESTIGATORS – 191578-003

Inv. ID No.	Principal Investigator	Subinvestigators	Address
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2294	Kerry Solomon, MD*		Medical University of SC Magill Laser Center 735 Johnny Dodds Blvd Mt. Pleasant, SC 29464
3754	Elizabeth Tonon, MD		Naval Medical Center Department of Ophthalmology 27 Effingham Street Portsmouth, VA 23708 Naval Medical Center Ophthalmology Clinic 620 John Paul Jones Circle Portsmouth, VA 23708
3755	John Wittpen, MD		Ophthalmic Consultants of Long Island 2500 Route 347, Bldg. 24 Stonybrook, NY 11790

*Included for completeness; these investigators or subinvestigators have Forms FDA 3455 attached

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration

Form Approved OMB No 0910-0396
Expiration Date 3/31/02

DISCLOSURE: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

The following information concerning Robert Snyder, M.D. (*Name of clinical investigator*), who participated as a clinical investigator in the submitted study 191578-002 Ketorolac Tromethamine Ophthalmic Solution 0.4% (*Name of clinical study*) is submitted in accordance with 21 CFR part 54. The named individual has participated in financial arrangements or holds financial interests that are required to be disclosed as follows:

Please mark the applicable checkboxes

- any financial arrangement entered into between the sponsor of the covered study and the clinical investigator involved in the conduct of the covered study, whereby the value of the compensation to the clinical investigator for conducting the study could be influenced by the outcome of the study;
- any significant payments of other sorts made on or after February 2, 1999 from the sponsor of the covered study such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria;
- any proprietary interest in the product tested in the covered study held by the clinical investigator;
- any significant equity interest as defined in 21 CFR 54.2(b), held by the clinical investigator in the sponsor of the covered study.

Details of the individual's disclosable financial arrangements and interests are attached, along with a description of steps taken to minimize the potential bias of clinical study results by any of the disclosed arrangements or interests.

NAME	TITLE
Eric Brandt	Corporate Vice President and Chief Financial Officer
FIRM/ORGANIZATION: Allergan, Inc.	
SIGNATURE	DATE: 2/10/02

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Rockville, MD 20857

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Public Health Service
Food and Drug Administration

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Expiration Date 3/31/02

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TO BE COMPLETED BY APPLICANT

The following information concerning Richard Lindstrom, M.D. (*Name of clinical investigator*), who participated as a clinical investigator in the submitted study 191578-003 Ketorolac (*Name of clinical study*) Tromethamine Ophthalmic Solution 0.4% is submitted in accordance with 21 CFR part 54. The named individual has participated in financial arrangements or holds financial interests that are required to be disclosed as follows:

Please mark the applicable checkboxes

- any financial arrangement entered into between the sponsor of the covered study and the clinical investigator involved in the conduct of the covered study, whereby the value of the compensation to the clinical investigator for conducting the study could be influenced by the outcome of the study,
- any significant payments of other sorts made on or after February 2, 1999 from the sponsor of the covered study such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria,
- any proprietary interest in the product tested in the covered study held by the clinical investigator;
- any significant equity interest as defined in 21 CFR 54.2(b), held by the clinical investigator in the sponsor of the covered study.

Details of the individual's disclosable financial arrangements and interests are attached, along with a description of steps taken to minimize the potential bias of clinical study results by any of the disclosed arrangements or interests

NAME	TITLE
Eric Brandt	Corporate Vice President and Chief Financial Officer
FIRM/ORGANIZATION: Allergan, Inc.	
SIGNATURE	DATE: 7/10/02

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration

Form Approved: OMB No. 0910-0396
Expiration Date: 3/31/02

DISCLOSURE: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

The following information concerning Frank Price, M.D. (*Name of clinical investigator*), who participated as a clinical investigator in the submitted study 191578-003 Ketorolac Tromethamine Ophthalmic Solution 0.4% (*Name of clinical study*), is submitted in accordance with 21 CFR part 54. The named individual has participated in financial arrangements or holds financial interests that are required to be disclosed as follows:

Please mark the applicable checkboxes.

- any financial arrangement entered into between the sponsor of the covered study and the clinical investigator involved in the conduct of the covered study, whereby the value of the compensation to the clinical investigator for conducting the study could be influenced by the outcome of the study;
- any significant payments of other sorts made on or after February 2, 1999 from the sponsor of the covered study such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria,
- any proprietary interest in the product tested in the covered study held by the clinical investigator,
- any significant equity interest as defined in 21 CFR 54.2(b), held by the clinical investigator in the sponsor of the covered study.

Details of the individual's disclosable financial arrangements and interests are attached, along with a description of steps taken to minimize the potential bias of clinical study results by any of the disclosed arrangements or interests.

NAME	TITLE
Eric Brandt	Corporate Vice President and Chief Financial Officer
FIRM/ORGANIZATION: Allergan, Inc.	
SIGNATURE	DATE: 7/10/02

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5600 Fishers Lane, Room 14-72
Rockville, MD 20857

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration

Form Approved. OMB No 0910-0396
Expiration Date. 3/31/02

DISCLOSURE: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

The following information concerning Kerry Solomon, M.D. (*Name of clinical investigator*), who participated as a clinical investigator in the submitted study 191578-003 Ketorolac Tromethamine Ophthalmic Solution 0.4% (*Name of clinical study*) is submitted in accordance with 21 CFR part 54. The named individual has participated in financial arrangements or holds financial interests that are required to be disclosed as follows:

Please mark the applicable checkboxes

- any financial arrangement entered into between the sponsor of the covered study and the clinical investigator involved in the conduct of the covered study, whereby the value of the compensation to the clinical investigator for conducting the study could be influenced by the outcome of the study;
- any significant payments of other sorts made on or after February 2, 1999 from the sponsor of the covered study such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria;
- any proprietary interest in the product tested in the covered study held by the clinical investigator,
- any significant equity interest as defined in 21 CFR 54.2(b), held by the clinical investigator in the sponsor of the covered study.

Details of the individual's disclosable financial arrangements and interests are attached, along with a description of steps taken to minimize the potential bias of clinical study results by any of the disclosed arrangements or interests.

NAME	TITLE
Eric Brandt	Corporate Vice President and Chief Financial Officer
FIRM/ORGANIZATION: Allergan, Inc.	
SIGNATURE	DATE: 7/10/02

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5600 Fishers Lane, Room 14-72
Rockville, MD 20857

FORM FDA 3455 (7/01)

Pre-NDA Meeting Minutes **May 20, 2002**

[redacted] Ketorolac Tromethamine Ophthalmic Solution 0.4%

FDA Attendees	Allergan Attendees
Jonca Bull	Scott Whitcup
Wiley Chambers	Janet Cheetham
Lee Simon	Peter Kresel
Jennifer Harris	Elizabeth Bancroft
William Boyd	L. Bland
Lucious Lim	T. Carpenter
Lisa Hubbard	L. Cleary
Carmen DeBellas	J. Fleitman
Stan Lin	T. Kuan
Jyoti Zalkikar	R. Schiffman
Zhou Chen	K.Stern
Linda Ng	
Josie Yang	
Lori Gorski	
Mike Puglisi	
Raphael Rodriguez	

Questions for Discussion

Overall

1. Allergan intends to submit the NDA in electronic format in compliance with the FDA Guidance for Industry "Providing Regulatory Submissions in Electronic Format- NDAs". Allergan will also provide the Agency with a paper review copy of the NDA submission. Electronic word documents will be submitted where feasible.

Chemistry

There are no chemistry topics for discussion.

Microbiology

1. There are no microbiology topics for discussion.

2. Preservative Efficacy data, Sterility Test validation data and Aseptic Process Validation data will be included in the Microbiology section. Please confirm that this is acceptable.

Response: Acceptable

Preclinical

1. Since changes in the new formulation of ketorolac tromethamine ophthalmic solution 0.4% were limited to reductions in concentrations of ketorolac (0.4% vs. 0.5%), benzalkonium chloride (0.006% vs. 0.010%), EDTA (0.015% vs. 0.10%) and octoxynol-40 ([redacted]) compared to the currently marketed formulation, no additional nonclinical toxicology studies of the ketorolac tromethamine ophthalmic solution 0.4% were judged to be necessary or were conducted to support the NDA submission. Please confirm that this is acceptable.

Response: We agree with the sponsor that the nonclinical toxicological studies are not necessary for this NDA submission.

2. Since there are no new nonclinical pharmacology, PK or toxicology studies for this reformulation, Allergan intends to cross-reference the Ketorolac Tromethamine 0.5% Ophthalmic Solution NDA (NDA 19-700, ACULAR), and to provide only overall nonclinical pharmacology, PK (ADME) and toxicology summaries without individual study summaries or tabular summaries. Please confirm that this is acceptable.

Response: Yes, it is acceptable.

Ketorolac Reformulation	ACULAR® Formulation
Ketorolac tromethamine 0.4%	Ketorolac tromethamine 0.5%
Benzalkonium chloride 0.006%	Benzalkonium chloride 0.010%
Edetate disodium 0.015%	Edetate disodium 0.10%
Octoxynol ([redacted]	Octoxynol [redacted]

Clinical/Biostatistics

1. Both clinical studies demonstrated clinically and statistically significant between-group differences favoring ketorolac in the primary efficacy endpoint, as well as secondary endpoints. Please confirm that these results satisfy the FDA requirement for demonstrating efficacy with this new formulation

Response: The response to this question can not be made based on the contents of the meeting package submitted.

Clinical significance for this product may be demonstrated by showing a 1-unit difference in the mean severity scores between the two groups. Alternatively, a statistically significant difference in the patients that have "no pain" is a clinically meaningful endpoint.

Note: The sponsor is also reminded that all efficacy and safety analysis submitted in the NDA should be conducted with and with out the data from Frank Bishop, MD.

2. As previously discussed with the FDA, investigator # 3508 in study 191578-003 had a portion of the escape medication ([redacted]) diverted. To assess whether this incident has any impact on the data, a sensitivity analysis was conducted. The pain intensity for the ITT population was analyzed with and without the data from this site. The between-group differences remained significant. Please confirm that this analysis satisfactorily addresses the FDA request for analyses and any concerns for data from this site.

Response: Concur

3. Allergan plans to submit a Pediatric Study Waiver for this NDA based on the proposed indication of "relief of pain following photorefractive keratectomy (PRK)" and the Pediatric Study Report which was done with ketorolac tromethamine 0.5% and approved by the agency on February 8, 2002 for NDA 19- 700 / ACULAR® and NDA 20-811/ACULAR®PF. Please comment.

Response: Concur

4. The pooled analysis template table shells can be found in this package behind the ISS and SE Table Shell tabs. Please review and confirm that these analyses are adequate for the NDA.

Response: Concur

5. Allergan proposes not to include Individual Patient Data Listings under Appendix 16.4 as per CH E3 in the final study reports or NDA Item 11, Case Report Tabulations. In place of Appendix 16.4, Allergan will provide electronic SAS Transport Files for all data sets in Item 11 of the NDA. Please confirm that this is acceptable-

Response: The division requests that Allergan submit the Individual Patient Data Listings as a hard copy or electronically as a PDF file.

[redacted] Ketorolac Tromethamine Ophthalmic Solution 0.5%
Telecon May 23, 2001

Questions for Discussion

1. Allergan is developing a new formulation of ACULAR@. The new formulation consists of the following changes from the currently approved formulation (NDA 19- 700) as follows:

New Formulation	ACULAR@ Formulation
Ketorolac tromethamine 0.4%	Ketorolac tromethamine 0.5%
Benzalkonium chloride 0.006%	Benzalkonium chloride 0.010%
Edetate disodium 0.015%	Edetate disodium 0.10%
Octoxynol [redacted]	Octoxynol [redacted]

Please confirm the acceptability of this formulation.

Reviewer's Comment:

Formulation is acceptable. Would the stability data in the NDA be generated from this new formulation. (LN)

2. Since the new formulation is very similar to the currently approved formulation, Allergan would like to propose conducting one Phase 3 clinical trial in support of the ketorolac tromethamine 0 4% ophthalmic solution NDA submission instead of two Phase 3 studies. Please comment on this possibility If one study is acceptable to the Agency, would the requirement for the sample size be different?

Reviewer's Comments:

The current Acular formulation is not approved for this indication therefore efficacy would have to be shown by conducting two (2) reproducible clinical trials with the new formulation. Alternatively, a three arm study with the new formulation, Acular PF and vehicle could be performed. Safety data from the current formulation would be able to be used in the review of the proposed 0 4% formulation. (JH)

3. The overall study design is a multi-center, randomized, double-masked, vehicle-controlled study with two parallel treatment groups Patients will be assigned to receive either ketorolac 0.4% or ketorolac vehicle. See section 4.0 of the protocol. Please confirm the acceptability of the overall design and treatment groups.

Reviewer's Comments: Acceptable. (JH)

4. Approximately 150 patients who are candidates for unilateral photorefractive keratectomy (PRK) will be enrolled at 5-8 sites. See sections 5.1,5.2 and 5.3 for details of the study population and selection criteria. Please confirm the acceptability of the study population.

Reviewer's Comments: Please provide clarification on inclusion criteria 3 & 4 and exclusion criteria #2,3,4,5,6,8 & 9. (JH)

5. The primary efficacy variable will be pain intensity during the second 6-hour post PRK period, and the secondary efficacy variables will include: pain intensity at other time periods, pain relief, escape medication usage and ocular symptoms. See sections 6.1.1.1 .and 6.1.1.2. Allergan proposes the use of 5-point scales for the assessment of pain intensity and pain relief collected in a patient diary, as outlined in Attachment 13.2 of the protocol. The criteria for effectiveness will be based on clinically and statistically significant between- group differences (section 6.1.2). Please confirm the acceptability of the efficacy response measures.

Reviewer's Comments:

The primary efficacy variable is not acceptable. It would only support 12 hours of dosing. Additionally, the sponsor should provide the agency with further clarification on how pain intensity will be recorded if the patient uses escape medication or if the patient experiences multiple bouts of pain during the evaluation period. (section 10.2). (JH)
Clinical efficacy needs to be defined.

6. The safety variables include adverse events, visual acuity, and biomicroscopy (see section 6.2). Please confirm the acceptability of these safety measures.

Reviewer's Comments: Acceptable. (JH)

7. The dosing regimen for Day 0 (Section 4) will include, one dose of masked study treatment (ketorolac or vehicle) immediately post-operative, three hours post-operative, and then every four hours while awake, not to exceed four doses on the day of surgery. On days 1-3 the regimen will be QID; dosing of the masked medication may be discontinued early in the event of pain intensity = 0. OCUFLOX@ will be administered 5 minutes prior to the masked medication at each time point. [redacted] will be provided as an escape medication since this is a vehicle-controlled study. See sections 7.1 -7.2 Please confirm the acceptability of this dosing regimen.

Reviewer's Comments: Acceptable. (JH)

8. Post-operatively, patient visits will occur daily until complete re-epithelialization has occurred. See section 8.4.1. Please confirm the schedule of visits and procedures.

Reviewer's Comments: Acceptable. (JH)

9. Section 10 0 outlines the statistical analyses planned. Please confirm the acceptability of this plan.

Reviewer's Comments:
The agency highly recommends that analyses be carried out on the per-protocol population and the intent-to -treat population. The sponsor should provide further rationale for the proposed safety population analysis. (JH)

10. Allergan is considering the use of electronic patient diaries to capture the primary efficacy data. Please comment on the acceptability of this proposed electronic data capture.

Reviewer's Comments: Acceptable. (JH)

Questions for Discussion

1. Allergan is developing a new formulation of ACULAR@. The new formulation consists of the following changes from the currently approved formulation (NDA 19- 700) as follows:

New Formulation	ACULAR@ Formulation
Ketorolac tromethamine 0.4%	Ketorolac tromethamine 0.5%
Benzalkonium chloride 0.006%	Benzalkonium chloride 0.010%
Edetate disodium 0.015%	Edetate disodium 0.10%
Octoxynol —	Octoxynol —

Please confirm the acceptability of this formulation.

Reviewer's Comment:

Formulation is acceptable. Would the stability data in the NDA be generated from this new formulation. How much data — 6 months, — prefirmed 1 year

2. Since the new formulation is very similar to the currently approved formulation, Allergan would like to propose conducting one Phase 3 clinical trial in support of the ketorolac tromethamine 0.4% ophthalmic solution NDA submission instead of two Phase 3 studies. Please comment on this possibility. If one study is acceptable to the Agency, would the requirement for the sample size be different?

Reviewer's Comments:

The current Acular formulation is not approved for this indication therefore efficacy would have to be shown by conducting two (2) reproducible clinical trials with the new formulation. Alternatively, a three arm study with the new formulation, Acular PF and vehicle could be performed. Safety data from the current formulation would be able to be used in the review of the proposed 0.4% formulation. — min. requirement — Safety NC

3. The overall study design is a multi-center, randomized, double-masked, vehicle-controlled study with two parallel treatment groups. Patients will be assigned to receive either ketorolac 0.4% or ketorolac vehicle. See section 4.0 of the protocol. Please confirm the acceptability of the overall design and treatment groups.

Reviewer's Comments:

Acceptable.

4. Approximately 150 patients who are candidates for unilateral photorefractive keratectomy (PRK) will be enrolled at 5-8 sites. See sections 5.1,5.2 and 5.3 for details of the study population and selection criteria. Please confirm the acceptability of the study population.

Reviewer's Comments:

Please provide clarification on inclusion criteria 3 & 4 and exclusion criteria #2,3,4,5,6,8 & 9.

5. The primary efficacy variable will be pain intensity during the second 6-hour post PRK period, and the secondary efficacy variables will include: pain intensity at other time periods, pain relief, escape medication usage and ocular symptoms. See sections 6.1.1.1 .and 6.1.1.2. Allergan proposes the use of 5-point scales for the assessment of pain intensity and pain relief collected in a patient diary, as outlined in Attachment 13.2 of the protocol. The criteria for effectiveness will be based on clinically and statistically significant between- group differences (section 6.1.2). Please confirm the acceptability of the efficacy response measures.

Reviewer's Comments:

The primary efficacy variable is not acceptable. It would only support 12 hours of dosing. Additionally, the sponsor should provide the agency with further clarification on how pain intensity will be recorded if the patient uses escape medication or if the patient experiences multiple bouts of pain during the evaluation period. (section 10.2).

Clinical efficacy needs to be defined.

6 The safety variables include adverse events, visual acuity, and biomicroscopy (see section 6.2) Please confirm the acceptability of these safety measures.

Reviewer's Comments:

Acceptable

7. The dosing regimen for Day 0 (Section 4) will include, one dose of masked study treatment (ketorolac or vehicle) immediately post-operative, three hours post-operative, and then every four hours while awake, not to exceed four doses on the day of surgery. On days 1-3 the regimen will be QID; dosing of the masked medication may be discontinued early in the event of pain intensity = 0. [redacted] will be administered 5 minutes prior to the masked medication at each time point. [redacted] will be provided as an escape medication since this is a vehicle-controlled study. See sections 7.1 -7.2. Please confirm the acceptability of this dosing regimen.

Reviewer's Comments:

Acceptable.

8. Post-operatively, patient visits will occur daily until complete re-epithelialization has occurred. See section 8.4.1. Please confirm the schedule of visits and procedures.

Reviewer's Comments:

Acceptable.

9. Section 10.0 outlines the statistical analyses planned. Please confirm the acceptability of this plan.

Reviewer's Comments:

The agency highly recommends that analyses be carried out on the per-protocol population and the intent-to -treat population. The sponsor should provide further rationale for the proposed safety population analysis. mp protocol, LOCF, ITT, submission

10. Allergan is considering the use of electronic patient diaries to capture the primary efficacy data. Please comment on the acceptability of this proposed electronic data capture.

Reviewer's Comments:

Acceptable.

LERGAN

upont Drive, P O Box 19534, Irvine, California, USA 92623-9534 Telephone (714) 246-4500 Website www.allergan.com

NDA ORIG AMENDMENT
BS

September 26, 2002

Raphael Rodriguez.
Project Manager
Division of Anti-Inflammatory, Analgesic,
& Ophthalmologic Drug Products, HFD-550
Food & Drug Administration
9201 Corporate Blvd. Building 2
Rockville, MD 20850

RE: Ketorolac tromethamine ophthalmic solution 0.4%
Statistical amendment, NDA 21-528

Dear Raphael,

Reference is made to the e-mail request received from you on September 23, 2002. The request was from Dr. Lu, the statistical reviewer, asking for Kaplan-Meier curves for data on time to first use of escape medication in each primary study.

Enclosed please find the two curves requested, one for each study.

Should you have any questions regarding this application or require any additional information, please contact me by telephone at (714) 246-4391, by fax at (714) 246-4272 or e-mail at bancroft_elizabeth@allergan.com.

Sincerely,

Elizabeth Bancroft
Senior Director
Regulatory Affairs

ERGAN

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NDA ORIG AMENDMENT
BL

September 27, 2002

RECEIVED
SEP 3 0 2002
MEGA/CDER

Wiley A. Chambers, M.D.
Deputy Director
Division of Anti-Inflammatory, Analgesic,
and Ophthalmic Drug Products, HFD-550
Food and Drug Administration
9201 Corporate Blvd. Building 2
Rockville, MD 20850

Re: NDA 21-528 / Ketorolac Tromethamine Ophthalmic Solution 0.4%
Amendment to A Pending New Drug Application – Proposed Tradename

Dear Dr. Chambers:

Reference is made to the New Drug Application NDA 21-528 submitted to the Agency on August 6, 2002 for Ketorolac Tromethamine Ophthalmic Solution 0.4%. As mentioned in the original NDA cover letter, Allergan had not yet finalized a proposed tradename at the time of filing but anticipated submitting a proposed tradename within 120 days of the submission. This amendment proposes a tradename for the new ketorolac tromethamine product.

Allergan proposes a tradename for Ketorolac Tromethamine Ophthalmic Solution 0.4% of:

ACULAR® — (ketorolac tromethamine ophthalmic solution) 0.4%.

We ask that the Agency review and comment on this proposed tradename and include this information in NDA 21-528. Should you have any questions regarding this submission or require any additional information, please contact me by telephone at (714) 246-4391, by fax at (714) 246-4272 or e-mail at bancroft_elizabeth@allergan.com.

Sincerely,

Elizabeth Bancroft
Senior Director
Regulatory Affairs

DUPLICATE

LLERGAN

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ORIG AMENDMENT

Bm

October 15, 2002

Raphael Rodriguez.
Project Manager
Division of Anti-Inflammatory, Analgesic,
& Ophthalmologic Drug Products, HFD-550
Food & Drug Administration
9201 Corporate Blvd. Building 2
Rockville, MD 20850

RE: Ketorolac tromethamine ophthalmic solution 0.4%
Clinical amendment, NDA 21-528

Dear Raphael,

Reference is made to the e-mail request received on October 9, 2002. The request was from Dr. Lim, the clinical reviewer, and is repeated below.

Question

Volume 15, page 285 (Table 14.6-1) contains an analysis on visual acuity at last visit: number (%) of patients with change from baseline (safety population). If a similar analysis was performed on data that excluded investigator 3753, please identify where it is located in the submission. Please perform such an analysis if it has not been performed.

Response

The requested information can be found in Table 14.6-27 (Visual Acuity at last Visit: Number (Percent) of Patient with Change from Baseline excluding Investigator 3753), Volume 15, page 307. This is from clinical study report 191578-002.

Should you have any questions regarding this application or require any additional information, please contact me by telephone at (714) 246-4391, by fax at (714) 246-4272 or e-mail at bancroft_elizabeth@allergan.com.

Sincerely,

Elizabeth Bancroft

Elizabeth Bancroft
Senior Director
Regulatory Affairs

ALLERGAN

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BS ORIG AMENDMENT

October 15, 2002

Raphael Rodriguez.
Project Manager
Division of Anti-Inflammatory, Analgesic,
& Ophthalmologic Drug Products, HFD-550
Food & Drug Administration
9201 Corporate Blvd. Building 2
Rockville, MD 20850

RECEIVED
OCT 16 2002
MEGA/CDER

RE: Ketorolac tromethamine ophthalmic solution 0.4%
Statistical amendment, NDA 21-528

Dear Raphael,

Reference is made to the e-mail request received on October 9, 2002. The request was from Dr. Lu, the statistical reviewer, and is repeated below.

Question
I'd like to clarify with Allergan for the reason why the number of patients with pain intensity measured immediately after surgery is smaller than that being randomized (98 vs 156 in Study 002, 138 vs 157 in Study 003). This information is based on Sponsor's Table 14.1-8 in both studies.

Response
Only patients who recorded a pain intensity rating (non-missing) immediately post-surgery and prior to the 1st dose of study medication were included in Table 14.1-8. All but 3 of the patients missing pain intensity at this time point were patients who did not record pain intensity prior to their 1st dose. Instead, these patients had already taken their 1st dose before attempting to record their pain intensity. A detailed explanation is attached.

Should you have any questions regarding this application or require any additional information, please contact me by telephone at (714) 246-4391, by fax at (714) 246-4272 or e-mail at bancroft_elizabeth@allergan.com.

Sincerely,

Elizabeth Bancroft
Senior Director
Regulatory Affairs

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LERGAN

ORIGINAL

Dupont Drive, P.O Box 19534, Irvine, California, USA 92623-9534 Telephone: (714) 246-4500 Website: www.allergan.com

October 16, 2002

Raphael Rodriguez.
Project Manager
Division of Anti-Inflammatory, Analgesic,
& Ophthalmologic Drug Products, HFD-550
Food & Drug Administration
9201 Corporate Blvd. Building 2
Rockville, MD 20850

RECEIVED
OCT 1 8 2002
MEGA/CDER

RE: Ketorolac tromethamine ophthalmic solution 0.4%
Microbiological amendment, NDA 21-528

B1
ORIG AMENDMENT

Dear Raphael,

Reference is made to the telephone conference between Vinayak Pawar, HFD-805, and Allergan on October 9, 2002 to discuss questions about Section 7, Microbiology, Aseptic Process, Report VR-V38-PSO-01-P196 Rev.00, Filter Validation. This report is located in the original NDA, paper volume 10, beginning on page 249. The questions and responses are included below.

Question 1
[This question refers to original NDA Section 7, paper volume 10, page 266]

Table 7.2.2.3-3 (page 17 of the filter validation report) gives the bacterial challenge recovery results for the filters. Dr. Pawar was unclear if the 3 CFU reported in the table were the actual CFU recovered from the 0.45μm control filter or the number of filters. If these were CFU recovery, he commented that *P. diminuta* should have passed through this filter and the counts should have been higher than 3.

Response
Table 7.2.2.3-3 contains the correct value for the recovery of the challenge microorganism as [redacted] The stated criteria in the study for the [redacted] control filter is that it must allow penetration of the challenge organism, *Pseudomonas diminuta*. The study protocol did not include quantitative limits for recovery of the challenge organism from the control filter.

The [redacted]

Because of these findings, future filter validation protocols will require that the maximum BP used for challenge control 0.45μm filters not exceed 38 psi[1].

Question 2

[This question refers to original NDA Section 7, paper volume 10, page 270]

Table 7.2.5.3 (page 22 of the filter validation report) Bubble Point Filter Integrity Results. Dr. Pawar wanted confirmation of the following interpretation of the data presented in this table: the first bubble point challenge data did not meet the criteria stated – there is an out of specification (OOS) value reported in the table.

Response

Table 7.2.5.3. (page 22 of the report) does not contain an OOS value. The data are the experimental test data used to calculate the minimum product-wetted bubble point (BP) limit for use in routine integrity testing, pre- and post-use, for water-wetted, product-wetted and 70% IPA-wetted filters. The calculated product-wetted and IPA-wetted (——— respectively) BP limits were derived using a formula which correlates the experimental test data to the established minimum water-wetted BP limit —— for the specified filter. The formula and calculations are taken from PDA Technical Report No. 26[2].

The results of the study showed significant variation (10% RSD) in the product-wetted BP test values, therefore the manufacturer's calculated minimum product-wetted BP is not appropriate for use as a BP limit to determine filter integrity. In addition, filters with lower product-wetted BP values than the manufacturer's calculated minimum product bubble point ———) have been shown capable of producing sterile filtrates based on bacterial challenge results.

All filters used in the determinations were considered integral pre- and post-use. Integrity tests were repeated for all filters using 70% IPA (isopropyl alcohol) as wetting agent after exposure to product. Test results are consistent with the manufacturer's established IPA-wetted bubble point limit of 18 psi[3].

Based on the results of the study, Allergan will only use water as a wetting agent for bubble point testing, pre- and post- use, for sterile filtration of ketorolac tromethamine 0.4%. This value is ———

References

1) Sartorius Memo, Project 01-01019, October 14, 2002

2) PDA Journal of Pharmaceutical Science and Technology, Technical Report No. 26, Sterilizing Filtration of Liquids. 1998 Supplement, Volume 52, Number S1

3) [redacted]

Should you have any questions regarding this application or require any additional information, please contact me by telephone at (714) 246-4391, by fax at (714) 246-4272 or e-mail at bancroft_elizabeth@allergan.com.

Sincerely,

Elizabeth Bancroft

Elizabeth Bancroft
Senior Director
Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

LERGAN

Dupont Drive, P O Box 19534, Irvine, California, USA 92623-9534 Telephone (714) 246-4500 Website www allergan com

October 18, 2002

Raphael Rodriguez.
Project Manager
Division of Anti-Inflammatory, Analgesic,
& Ophthalmologic Drug Products, HFD-550
Food & Drug Administration
9201 Corporate Blvd. Building 2
Rockville, MD 20850

RE: Ketorolac tromethamine ophthalmic solution 0.4%
Statistical amendment, NDA 21-528

Dear Raphael,

Reference is made to the e-mail request received on October 17, 2002. The request was from Dr. Lu, the statistical reviewer, and is repeated below.

Question
I just found out that there was no information provided for the 0-3 hour and 3-6 hour periods in the Kaplan-Meier curves sent by the sponsor. Could you please ask them to add those information to the curves?

Response

The figures showing the Kaplan-Meier curves for both (1) time to first zero pain intensity and (2) time to first use of escape medication for both studies (191578-002 and -003) have been updated to include the time interval from 0 to 6 hours. The plotted values are in the corresponding tables 14.2-1.2 and 14.2-3.3, respectively, in the clinical study reports. However, the time intervals are in 6-hour increments, as stated in the prospective analysis plan.

The figures for 191578-002 and -003 are attached.

Should you have any questions regarding this application or require any additional information, please contact me by telephone at (714) 246-4391, by fax at (714) 246-4272 or e-mail at bancroft_elizabeth@allergan.com.

Sincerely,

Elizabeth Bancroft
Senior Director
Regulatory Affairs

LLERGAN

5 Dupont Drive, P O Box 19534, Irvine, California, USA 92623-9534 Telephone (714) 246-4500 Website www allergan com

October 18, 2002

ORIG AMENDMENT
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RECEIVED
OCT 2 1 2002
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Wiley A. Chambers, M.D.
Deputy Director
Division of Anti-Inflammatory, Analgesic,
and Ophthalmic Drug Products, HFD-550
Food and Drug Administration
9201 Corporate Blvd. Building 2
Rockville, MD 20850

Re: NDA 21-528 / Ketorolac Tromethamine Ophthalmic Solution 0.4%
Amendment to A Pending New Drug Application – Proposed Tradename

Dear Dr. Chambers:

Reference is made to the New Drug Application NDA 21-528 submitted to the Agency on August 6, 2002 for Ketorolac Tromethamine Ophthalmic Solution 0.4%. Reference is also made to the September 27, 2002 Amendment to A Pending New Drug Application – Proposed Tradename and the October 16th and 18th, 2002 telephone conversations between Allergan and Dr. Su Tso, FDA Review Chemist regarding an explanation for the additional letters in the proposed tradename. This amendment provides an explanation.

Allergan proposes a tradename for Ketorolac Tromethamine Ophthalmic Solution 0.4% of:

ACULAR® — (ketorolac tromethamine ophthalmic solution) 0.4%.

The — abbreviation in the proposed new tradename stands for —

We ask that the Agency review and comment on this proposed tradename and include this information in NDA 21-528. Should you have any questions regarding this submission or require any additional information, please contact me by telephone at (714) 246-4391, by fax at (714) 246-4272 or e-mail at bancroft_elizabeth@allergan.com.

Sincerely,

Elizabeth Bancroft

Elizabeth Bancroft
Senior Director
Regulatory Affairs

cc: Dr. S. Tso

ORIGINAL

ALLERGAN

BC

P O Box 19534 Irvine California, USA 92623-9534 Telephone (714) 246-4500 Website www.allergan.com

November 4, 2002

Raphael Rodriguez.
Project Manager
Division of Anti-Inflammatory, Analgesic,
& Ophthalmologic Drug Products, HFD-550
Food & Drug Administration
9201 Corporate Blvd. Building 2
Rockville, MD 20850

RE: NDA 21-528 Ketorolac tromethamine ophthalmic solution 0.4%
Chemistry amendment

Dear Mr. Rodriguez,

Reference is made to the fax received on October 11, 2002 from Dr. Su Tso, Chemistry Reviewer. The questions and responses are provided in the attached documents. We believe we have fully responded to all the questions.

Should you have any questions regarding this application or require any additional information, please contact me by telephone at (714) 246-4391, by fax at (714) 246-4272 or e-mail at bancroft_elizabeth@allergan.com.

Thank you for your assistance with this application.

Sincerely,

Elizabeth Bancroft

Elizabeth Bancroft
Senior Director
Regulatory Affairs

ERGAN

pont Drive, P O Box 19534, Irvine, California, USA 92623-9534 Telephone (714) 246-4500 Website www allergan com

November 12, 2002

Wiley A. Chambers, M.D.
Deputy Director
Division of Anti-Inflammatory, Analgesic,
and Ophthalmic Drug Products, HFD-550
Food and Drug Administration
9201 Corporate Blvd. Building 2
Rockville, MD 20850

Re: NDA 21-528 / Ketorolac Tromethamine Ophthalmic Solution 0.4%
Amendment to A Pending New Drug Application – Proposed Alternative Tradename

Dear Dr. Chambers:

Reference is made to the New Drug Application NDA 21-528 submitted to the Agency on August 6, 2002 for Ketorolac Tromethamine Ophthalmic Solution 0.4% and to the amendments of September 27, 2002 and October 18, 2002. Reference is also made to the November 1, 2002 e-mail from Raphael Rodriguez regarding the unacceptability of Allergan's original proposed tradename. This amendment proposes an alternative tradename.

Allergan proposes an alternative tradename for Ketorolac Tromethamine Ophthalmic Solution 0.4% of:

ACULAR® — (ketorolac tromethamine ophthalmic solution) 0.4%.

The —' in the proposed new tradename is not intended to be an abbreviation of any other word.

We ask that the Agency review and comment on this proposed alternative tradename and include this information in NDA 21-528. Should you have any questions regarding this submission or require any additional information, please contact me by telephone at (714) 246-4391, by fax at (714) 246-4272 or e-mail at bancroft_elizabeth@allergan.com.

Sincerely,

Elizabeth Bancroft
Senior Director
Regulatory Affairs

cc: Dr. L. Lim

ALLERGAN

ORIGINAL

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December 6, 2002

Wiley A. Chambers, M.D.
Deputy Director
Division of Anti-Inflammatory, Analgesic,
and Ophthalmic Drug Products, HFD-550
Food and Drug Administration
9201 Corporate Blvd. Building 2
Rockville, MD 20850

Re: **NDA 21-528**
Ketorolac Tromethamine Ophthalmic Solution 0.4%
120-Day Safety Update

Dear Dr. Chambers:

Reference is made to the original New Drug Application NDA 21-528 for Ketorolac Tromethamine Ophthalmic Solution 0.4% submitted to the Agency on August 6, 2002. Pursuant to 21 CFR 314.50(d)(5)(vi)(b), Allergan is submitting the 120-Day Safety Update for Ketorolac Tromethamine Ophthalmic Solution 0.4%.

The pivotal Phase 3 studies in support of the original NDA, clinical studies 191578-002 and 191578-003, were completed and full study reports were submitted in the original submission. There are no additional safety data to report from these studies.

No new preclinical or clinical studies have been planned or conducted during this 120-Day reporting period.

Should you have any questions regarding this submission or require any additional information, please contact me by telephone at (714) 246-4391, by fax at (714) 246-4272 or e-mail at bancroft_elizabeth@allergan.com.

Sincerely,

Elizabeth Bancroft

Elizabeth Bancroft
Senior Director
Regulatory Affairs

ALLERGAN

ORIGINAL

25 Dupont Drive, P O Box 19534, Irvine, California, USA 92623-9534 Telephone (714) 246-4500 Website www.allergan.com

December 6, 2002

Wiley A. Chambers, M.D.
Deputy Director
Division of Anti-Inflammatory, Analgesic,
and Ophthalmic Drug Products, HFD-550
Food and Drug Administration
9201 Corporate Blvd. Building 2
Rockville, MD 20850

Re: **NDA 21-528**
Ketorolac Tromethamine Ophthalmic Solution 0.4%
120-Day Safety Update

Dear Dr. Chambers:

Reference is made to the original New Drug Application NDA 21-528 for Ketorolac Tromethamine Ophthalmic Solution 0.4% submitted to the Agency on August 6, 2002. Pursuant to 21 CFR 314.50(d)(5)(vi)(b), Allergan is submitting the 120-Day Safety Update for Ketorolac Tromethamine Ophthalmic Solution 0.4%.

The pivotal Phase 3 studies in support of the original NDA, clinical studies 191578-002 and 191578-003, were completed and full study reports were submitted in the original submission. There are no additional safety data to report from these studies.

No new preclinical or clinical studies have been planned or conducted during this 120-Day reporting period.

Should you have any questions regarding this submission or require any additional information, please contact me by telephone at (714) 246-4391, by fax at (714) 246-4272 or e-mail at bancroft_elizabeth@allergan.com.

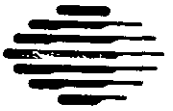
Sincerely,

Elizabeth Bancroft
Senior Director
Regulatory Affairs

LLERGAN

ORIG AMENDMENT

BC



Dupont Drive P O Box 19534 Irvine, California, USA 92623-9534 Telephone (714) 246-4500 Website www allergan com

December 23, 2002

RECEIVED
DEC 2 4 2002
MEGA/CDER

Raphael Rodriguez.
Project Manager
Division of Anti-Inflammatory, Analgesic,
& Ophthalmologic Drug Products, HFD-550
Food & Drug Administration
9201 Corporate Blvd. Building 2
Rockville, MD 20850

RE: NDA 21-528 Ketorolac tromethamine ophthalmic solution 0.4%
Chemistry amendment

Dear Mr. Rodriguez,

Reference is made to the fax received on December 13, 2002 from Dr. Su Tso, Chemistry Reviewer. The questions and responses are provided in the attached documents.

Should you have any questions regarding this application or require any additional information, please contact me by telephone at (714) 246-4391, by fax at (714) 246-4272 or e-mail at bancroft_elizabeth@allergan.com.

Thank you for your assistance with this application.

Sincerely,

Elizabeth Bancroft
Senior Director
Regulatory Affairs

ORIGINAL

ERGAN

pont Drive, P O Box 19534 Irvine, California, USA 92623-9534 Telephone (714) 246-4500 Website www allergan com

January 20, 2003

February 24, 2003

ORIG AMENDMENT

Raphael Rodriguez
Project Manager
Division of Anti-Inflammatory, Analgesic,
and Ophthalmic Drug Products, HFD-550
Food and Drug Administration
9201 Corporate Blvd. Building 2
Rockville, MD 20850

RECEIVED
FEB 2 5 2003
MEGA/CDER

Re: **NDA 21-528 / Ketorolac Tromethamine Ophthalmic Solution 0.4%**
Chemistry Amendment

Dear Mr. Rodriguez:

Reference is made to the facsimiles received on January 20, 2003 and February 13, 2003 from Dr. Su Tso, Chemistry Reviewer. The questions and responses are provided in the attached documents.

Should you have any questions regarding this application or require any additional information, please contact me by telephone at (714) 246-4391, by fax at (714) 246-4272 or e-mail at bancroft_elizabeth@allergan.com.

Thank you for your assistance with this application.

Sincerely,

Elizabeth Bancroft
Senior Director
Regulatory Affairs

DUPLICATE

1 004

LERGAN

ORIGINAL

pont Drive, P O Box 19534, Irvine, California, USA 92623-9534 Telephone (714) 246-4500 Website www.allergan.com

February 28, 2003

RECEIVED
MAR 0 3 2003
MEGA/CDER

Raphael Rodriguez
Project Manager
Division of Anti-Inflammatory, Analgesic,
and Ophthalmic Drug Products, HFD-550
Food and Drug Administration
9201 Corporate Blvd. Building 2
Rockville, MD 20850

Bc
ORIG AMENDMENT

Re: **NDA 21-528 / Ketorolac Tromethamine Ophthalmic Solution 0.4%**
Chemistry Amendment

Dear Mr. Rodriguez:

Reference is made to the February 26, 2003 and February 28, 2003 telephone conversations between Dr. Su Tso, Chemistry Reviewer, and myself regarding NDA 21-528.

Enclosed in Section 1, please find a copy of a Technical Memorandum containing pictures of the ketorolac container closure as requested by Dr. Tso in our telephone conversation of February 26th.

At this time, we would also like to clarify the word "exterior" in the last sentence of Allergan's response to Question 2, page 1 011, (FDA fax of January 20, 2003) in the Chemistry Amendment previously submitted on February 24, 2003.

The sentence reads "The yellow precipitate on the exterior of the stability samples does not compromise the chemistry or the container integrity (e.g. microbial contamination) of the product."

The word exterior means the exterior of the tip-bottle interface, under the closure cap.

Therefore, the sentence should read "The yellow precipitate on the exterior of the tip-bottle interface, under the closure cap of the stability samples does not compromise the chemistry or the container integrity (e.g. microbial cofitamination) of the product."

Section 2 contains a copy from the pending NDA of the Summary of BAK Titration Studies for Formulation 9437X as requested by Dr. Tso in our February 28th telephone conversation. This report is located in the original NDA in Section 7, Volume 10, (paper review copy) pages 10 056 - 10 089.

A desk copy of this submission has also been sent to Dr. Tso.

Should you have any questions regarding this submission or require any additional information, please contact me by telephone at (714) 246-4391, by fax at (714) 246-4272 or e-mail at bancroft_elizabeth@allergan.com.

Thank you for your assistance with this application.

Sincerely,

Elizabeth Bancroft
Senior Director
Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

LERGAN

ORIG AMENDMENT

BC

Dupont Drive P O Box 19534, Irvine California, USA 92623-9534 Telephone (714) 246-4500 Website www allergan com

April 2, 2003

Raphael Rodriguez
Project Manager
Division of Anti-Inflammatory, Analgesic,
& Ophthalmologic Drug Products, HFD-550
Food & Drug Administration
9201 Corporate Blvd. Building 2
Rockville, MD 20850

RECEIVED
APR 0 3 2003
MEGA/CDER

RE: NDA 21-528 Ketorolac tromethamine ophthalmic solution 0.4%
Chemistry Amendment

Dear Mr. Rodriguez,

Reference is made to NDA 21-528 and the correspondence of March 21, 2003 from Dr. Tso, Chemistry Reviewer.

Enclosed please find the chemistry information relating to the questions on container closures.

The following key statements should be considered:

1. All aseptically filled and sealed products unequivocally meet the chemical, physical, sterility and package integrity specifications throughout their shelf-life.

2. The ophthalmic container closure systems are manufactured by and conform to recognized and standard industry-wide practices and processes.

3. The validity of both the aseptic manufacturing process and packaging/microbial integrity is justified through validated container media fill runs. 100% testing of the filled/capped units occur, the results of which demonstrate that sterility is maintained and that no microbial ingress occur.

4. Any observed trace precipitate formation is a consequence of the presence of the inherent micro-imperfections occurring at the tip weld line. These trace precipitates always occur at the weld line, and is also the location observed with competitor product.

5. Precipitate formation occurs from an initial wetting of the tip weld line inside of the container closure system. Wetting occurs from 2 events. First, during handling/transportation of the filled and sealed product. At this point, liquid motion or a splashing effect inside the sealed container occurs as a response to movement of the container along the packaging line. Secondly, and to a lesser extent, the natural process of condensation can contribute to inner surface wetting. These 2 events cause

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a small residual amount of liquid inside the container to be held at the tip weld line due to surface tension/adhesion forces. At this point, capillary action ensues causing the residual liquid to travel along the micro-imperfections. This phenomenon is a slow process and supported by the fact that trace precipitation is not evident at product release (time zero).

6. Visibility of these sporadic trace precipitates is extremely difficult under normal viewing conditions. It was not until a highly colored (yellow) product, Ketorolac Reformulation (9437X), on a white tip background was examined, and the trace precipitate was seen. This event resulted in an increased level of scrutiny for Ketorolac Reformulation and at that juncture for all other products under development in R&D. A chronological summary of events is provided.

7. Media validation studies, sterility tests, aerosol challenge tests and vacuum leak tests confirmed that package integrity and sterility of products were never compromised. Notwithstanding, in order to better track and record trace precipitates, an —— investigation process (in conjunction with extraordinary observation methodologies) was used as the means for data collection.

8. Where sporadic trace precipitate formation occurred it was always under the sealed, sterile cap closure of the container.

9. Again, it can not be overstated that all the microbial challenge tests and package integrity tests support and justify that the quality and, indeed sterility, are maintained throughout product shelf-life.

Question 1

Please provide an in depth explanation for the observation of [redacted] at the tip-bottle interface under the closure cap of the stability samples at all time points and all temperature conditions regardless of the sample orientation (upright or inverted). Please provide a proposed correction plan to prevent and eliminate future occurrence.

Allergan Response

The following information is included in response to this question. The same information was submitted to NDA 21-493 as a chemistry amendment dated March 12, 2003. NDA 21-493 was approved on March 28, 2003.

Section 1	Chronology of R&D Trace Precipitate Observations (flow chart and summary)
Section 2	Packaging Development Summary of the Tip-Bottle Interface Technical Memorandum PDD-TM-03-013 – Mechanism of Precipitate Formation
Section 3	Results of Vacuum Leak Test (10 mL container ketorolac) Results of Sterility Testing (Brimonidine Combo Product) Results of Sterility Testing (Epinastine) Results of PSO Fill Line Media Qualification
Section 4	Package Integrity Testing of Allergan Ophthalmic Solution Containers (Dust Chamber Method) BTC Number 38209 (10 mL container)
Section 5	SOP LAB-03E Performing pH and Physical Appearance Tests SOP LAB-12E Evaluation and Disposition of Out of Specification (OOS) Results SOP LAB-24 Package Integrity and Fill Volume Testing SOP TPC-037 Vacuum Leak Test
Section 6	Proposed Correction Plan

Question 2

Please commit to place the first three production batches on stability, and modify the stability protocol to include a parameter to control package integrity (as a visual test) for the formation of [redacted].

Allergan Response

Allergan commits to place the first 3 production batches of ketorolac tromethamine ophthalmic solution 0.4% into ongoing stability. Allergan agrees to modify the stability protocol to include a parameter to monitor package integrity at each interval.

We trust that these responses are complete and adequate for approval. If you should require additional information, please contact me at telephone (714) 246-4391, fax (714) 246-4272, or email at bancroft_elizabeth@allergan.com.

Sincerely,

Elizabeth Bancroft
Sr. Director
Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

LERGAN

Dupont Drive, P O Box 19534, Irvine, California, USA 92623-9534 Telephone, (714) 246-4500 Website www allergan com

April 11, 2003

Raphael Rodriguez.
Project Manager
Division of Anti-Inflammatory, Analgesic,
& Ophthalmologic Drug Products, HFD-550
Food & Drug Administration
9201 Corporate Blvd. Building 2
Rockville, MD 20850

RE: NDA 21-528 Ketorolac tromethamine ophthalmic solution 0.4%
Proposed Draft Labeling

Dear Mr. Rodriguez,

Reference is made to the proposed draft labeling received from the Agency on March 5, 2003. Enclosed please find the Allergan comments on the proposed labeling.

Included are a draft package insert and an annotated draft package insert. We look forward to discussing this proposal with you.

Should you have any questions regarding this application or require any additional information, please contact me by telephone at (714) 246-4391, by fax at (714) 246-4272 or e-mail at bancroft_elizabeth@allergan.com.

Thank you for your assistance with this application.

Sincerely,

Elizabeth Bancroft
Senior Director
Regulatory Affairs

LERGAN

Dupont Drive, P O Box 19534, Irvine, California, USA 92623-9534 Telephone (714) 246-4500 Website www.allergan.com

April 29, 2003

N-000(BL)

RECEIVED
APR 3 0 2003
MEGA/CDER

Wiley A. Chambers, M.D.
Deputy Director
Division of Anti-Inflammatory, Analgesic,
and Ophthalmic Drug Products, HFD-550
Food and Drug Administration
9201 Corporate Blvd. Building 2
Rockville, MD 20850

Re: NDA 21-528 / Ketorolac Tromethamine Ophthalmic Solution 0.4%
Amendment to A Pending New Drug Application – Proposed Alternative Tradename and Draft Labeling

Dear Dr. Chambers:

Reference is made to the New Drug Application NDA 21-528 for Ketorolac Tromethamine Ophthalmic Solution 0.4% and to the tradename amendments of September 27, 2002, October 18, 2002 and November 12, 2002. Reference is also made to the proposed draft labeling received from the Agency on March 5, 2003, Allergan's response submitted to the Agency on April 11, 2003; to the April 21, 2003 teleconference in which proposed changes to the package insert were discussed with the Agency and to the April 28, 2003 videoconference called to discuss a different product at which the Agency informed Allergan of the unacceptability of Allergan's alternative proposed tradename ACULAR® — This amendment proposes another alternative tradename and includes draft labeling which incorporates the agreed upon changes to the package insert.

Allergan proposes an alternative tradename for Ketorolac Tromethamine Ophthalmic Solution 0.4% of:

ACULAR® LS™ (ketorolac tromethamine ophthalmic solution) 0.4%.

The "LS" abbreviation in the proposed new tradename stands for "Lower Strength". Allergan agrees to use only "Lower Strength" to define "LS" in any promotional materials.

DUPLICATE

Draft Package Insert

Appended in Section 1 is a copy of the draft package insert. The following revisions have been made:

1. Under "Description", the words "and Molecular" have been added to Structural Formula. Under the subsection Contains, 2nd paragraph; the word "approximately" has

been inserted into the first sentence before 7.4 and into the last sentence before 290 mOsml/kg.

2. Under "Clinical Pharmacology", Mechanism of Action, deleted the second paragraph.

3. Under "Clinical Pharmacology", Pharmacokinetics, deleted the first paragraph.

4. Under "Clinical Pharmacology", Clinical Studies, 1st paragraph, revised the last sentence to read "following photorefractive keratectomy surgery."

5. The "Indications and Usage" section has been revised to read "Tradename ophthalmic solution 0.4% is indicated for the reduction of ocular pain and ocular symptom of burning/stinging following corneal refractive surgery."

6. Under "Precautions", 1st paragraph, revised first sentence to include the words "including ketorolac tromethamine ophthalmic solution,"

7. Under "Precautions", subsection Carcinogenesis, Mutagenesis, Impairment of Fertility, 1st paragraph, added the word "either" before rats and changed the word "or" to "nor" in mice.

8. Under "Adverse Reactions", 1st paragraph, revised [redacted] " to "ocular edema" and "ocular pain." Re-ordered the adverse reactions.

9. Under "Adverse Reactions", 2nd paragraph, deleted the words " [redacted] " from the first sentence.

10. Under "Adverse Reactions", 3rd paragraph, deleted [redacted] changed [redacted] to "ocular pain" and re-ordered the adverse events.

11. Under "Adverse Reactions", 4th paragraph, Clinical Practice, deleted the [redacted] and added "s" to solution in the first and third sentences.

12. The "Dosage and Administration" section has been revised to read "The recommended dose of Tradename ophthalmic solution 0.4% is one drop four times a day in the operated eye as needed for pain and burning/stinging for up to 4 days following corneal refractive surgery."

13. Under "How Supplied", [redacted] fill size has been deleted and the statement has been revised to reflect one product size. The storage temperature has been revised to read "Store at 15° - 25°C (59°F - 77°F).

14. The statement " [redacted] " has been revised to read "This product is manufactured and distributed by ALLERGAN under license from its developer, Roche Palo Alto LLC, Palo Alto, California, U.S.A." The documentation for the name change which was sent to Allergan from Hoffmann La Roche is appended in Section 2.

We ask that the Agency review and comment on this proposed alternative tradename and draft package insert and include this information in NDA 21-528. Should you have any questions regarding this submission or require any additional information, please contact me by telephone at (714) 246-4391, by fax at (714) 246-4272 or e-mail at bancroft_elizabeth@allergan.com.

Sincerely,

Elizabeth Bancroft

Elizabeth Bancroft
Senior Director
Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

ALLERGAN

2525 Dupont Drive P O Box 19534, Irvine, California USA 92623-9534 Telephone (714) 246-4500 Website www.allergan.com

May 6, 2003

N-000(BL)

Wiley A. Chambers, M.D.
Deputy Director
Division of Anti-Inflammatory, Analgesic,
and Ophthalmic Drug Products, HFD-550
Food and Drug Administration
9201 Corporate Blvd. Building 2
Rockville, MD 20850

Re: NDA 21-528 / Ketorolac Tromethamine Ophthalmic Solution 0.4%
Amendment to A Pending New Drug Application – Final Draft Labeling

Dear Dr. Chambers:

Reference is made to Allergan's Amendment to A Pending New Drug Application – Proposed Alternative Tradename and Draft Labeling submitted to the Agency on April 29, 2003 and to the May 6, 2003 telephone conversation between Raphael Rodriguez and myself in which he requested a copy of the draft package insert with the proposed tradename ACULAR LS™ inserted in place of TRADENAME and some additional revisions to the Precautions section. This amendment contains the following labeling information in response to the Agency's request:

Final Draft Package Insert

Appended in Section 1 is a copy of the revised final draft package insert. The following additional revisions have been made:

Under "Precautions", subsection Carcinogenesis, Mutagenesis, Impairment of Fertility; the first paragraph has been revised to read "Ketorolac tromethamine was neither carcinogenic in rats given up to 5 mg/kg/day orally for 24 months (156 times the maximum recommended human topical ophthalmic dose, on a mg/kg basis, assuming 100% absorption in humans and animals) nor in mice given 2 mg/kg/day orally for 18 months (62.5 times the maximum recommended human topical ophthalmic dose, on a mg/kg basis, assuming 100% absorption in humans and animals).

Label and Carton

Section 2 contains a color copy of the proposed ACULAR LS™ 5 mL label and 5 mL unit carton.

We ask that the Agency review and approve this final draft package insert, label and carton and include this information in NDA 21-528. Should you have any questions regarding this submission or require any additional information, please contact me by telephone at (714) 246-4391, by fax at (714) 246-4272 or e-mail at bancroft_elizabeth@allergan.com.

Sincerely,

Elizabeth Bancroft

Elizabeth Bancroft
Senior Director
Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

ALLERGAN

2525 Dupont Drive, P.O. Box 19534, Irvine, California, USA 92623-9534 Telephone: (714) 246-4500 Website: www.allergan.com

May 9, 2003

Wiley A. Chambers, M.D.
Deputy Director
Division of Anti-Inflammatory, Analgesic,
and Ophthalmic Drug Products, HFD-550
Food and Drug Administration
9201 Corporate Blvd. Building 2
Rockville, MD 20850

Re: NDA 21-528 / Ketorolac Tromethamine Ophthalmic Solution 0.4%
Amendment to A Pending New Drug Application – Final Draft Labeling

Dear Dr. Chambers:

Reference is made to Allergan's Amendment to A Pending New Drug Application – Final Draft Labeling submitted to the Agency on May 6, 2003 and to the May 9, 2003 telephone conversation between Raphael Rodriguez and myself in which he requested an additional revision to the draft package insert for ACULAR LS™ This amendment contains the revised package insert in response to the Agency's request.

Final Draft Package Insert

Appended in Section 1 is the revised final draft package insert. The following additional revision has been made:

Under "Indications and Usage", the sentence has been revised to read "ACULAR LS™ ophthalmic solution is indicated for the reduction of ocular pain and the ocular symptom of burning / stinging following corneal refractive surgery."

We ask that the Agency review and approve this revised final draft package insert, and include this information in NDA 21-528. Should you have any questions regarding this submission or require any additional information, please contact me by telephone at (714) 246-4391, by fax at (714) 246-4272 or e-mail at bancroft_elizabeth@allergan.com.

Sincerely,

Elizabeth Bancroft
Senior Director
Regulatory Affairs

ALLERGAN

2525 Dupont Drive, P O Box 19534, Irvine, California, USA 92623-9534 Telephone (714) 246-4500 Website www allergan com

May 20, 2003

N-000(BF)

ORIG AMENDMENT

Wiley A. Chambers, M.D.
Deputy Director
Division of Anti-Inflammatory, Analgesic,
and Ophthalmic Drug Products, HFD-550
Food and Drug Administration
9201 Corporate Blvd. Building 2
Rockville, MD 20850

Re: NDA 21-528 / Ketorolac Tromethamine Ophthalmic Solution 0.4%
Amendment to A Pending New Drug Application – Final Draft Labeling

Dear Dr. Chambers:

Reference is made to Allergan's Amendment to A Pending New Drug Application – Final Draft Labeling submitted to the Agency on May 9, 2003 and to the May 12, 2003 telephone conversation between Dr. Lim and myself in which she requested additional revisions to the draft package insert, 5 mL label and 5 mL unit carton for ACULAR LS™. Reference is also made to the May 13, 2003 telephone conversation between Dr. Lim and Dave Garbe regarding tradename placement. This amendment contains the following revisions in response to the Agency's request:

Draft Package Insert

Appended in Section 1 is the revised draft package insert:

Under "Contains: Active:" added a period after "ketorolac tromethamine 0.4%."

Under "Indications and Usage", deleted the words ' [redacted] ' and revised the sentence to read "ACULAR LS™ ophthalmic solution is indicated for the reduction of ocular pain and burning / stinging following corneal refractive surgery."

Under "How Supplied", deleted the — between the 5 mL and 10 mL so that the line is revised to read "5 mL in 10 mL bottle – NDC 0023-9277-05".

5 mL Label / 5 mL Unit Carton

Allergan has revised the label and carton as discussed with Dr. Lim. A copy of the artwork for each piece is included in Section 2.

ORIGINAL

We ask that the Agency review and approve this revised final draft package insert and include this information in NDA 21-528. Should you have any questions regarding this submission or require any additional information, please contact me by telephone at (714) 246-4391, by fax at (714) 246-4272 or e-mail at bancroft_elizabeth@allergan.com.

Sincerely,

Elizabeth Bancroft
Senior Director
Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

ALLERGAN

• Dupont Drive, P O Box 19534, Irvine, California, USA 92623-9534 Telephone. (714) 246-4500 Website www allergan com

May 22, 2003

ORIGINAL

Wiley A. Chambers, M.D.
Deputy Director
Division of Anti-Inflammatory, Analgesic,
and Ophthalmic Drug Products, HFD-550
Food and Drug Administration
9201 Corporate Blvd. Building 2
Rockville, MD 20850

RECEIVED
MAY 23 2003
MEGA/CDER

Re: NDA 21-528 / Ketorolac Tromethamine Ophthalmic Solution 0.4%
Amendment to A Pending New Drug Application – Labeling Response

NEW CORRESP

Dear Dr. Chambers:

Reference is made to NDA 21-528 and the labeling amendment dated May 20, 2003. Reference is also made to the May 22, 2003 telephone conversation between Dr. Lim, myself and Dave Garbe regarding the ACULAR LS™ tradename placement on the label and unit carton. This amendment contains the following labeling commitment by Allergan:

Label / Unit Carton

Allergan commits to changing the prominence of the LS™ to mirror that of the word ACULAR on both the label and carton.

We ask that the Agency approve this labeling commitment and include this information in NDA 21-528. Should you have any questions regarding this submission or require any additional information, please contact me by telephone at (714) 246-4391, by fax at (714) 246-4272 or e-mail at bancroft_elizabeth@allergan.com.

Sincerely,

Elizabeth Bancroft
Senior Director
Regulatory Affairs