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P.O. Box 1450
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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
14/493,903	09/23/2014	Shirou SAWA	2014-1250

CONFIRMATION NO. 7395

513
WENDEROTH, LIND & PONACK, L.L.P.
1030 15th Street, N.W.,
Suite 400 East
Washington, DC 20005-1503

PUBLICATION NOTICE

OC00000072741374

Title:AQUEOUS LIQUID PREPARATION CONTAINING 2-AMINO-3-(4-BROMOBENZOYL)PHENYLACETIC ACID

Publication No.US-2015-0011634-A1
Publication Date:01/08/2015

NOTICE OF PUBLICATION OF APPLICATION

The above-identified application will be electronically published as a patent application publication pursuant to 37 CFR 1.211, et seq. The patent application publication number and publication date are set forth above.

The publication may be accessed through the USPTO's publically available Searchable Databases via the Internet at www.uspto.gov. The direct link to access the publication is currently http://www.uspto.gov/patft/.

The publication process established by the Office does not provide for mailing a copy of the publication to applicant. A copy of the publication may be obtained from the Office upon payment of the appropriate fee set forth in 37 CFR 1.19(a)(1). Orders for copies of patent application publications are handled by the USPTO's Office of Public Records. The Office of Public Records can be reached by telephone at (703) 308-9726 or (800) 972-6382, by facsimile at (703) 305-8759, by mail addressed to the United States Patent and Trademark Office, Office of Public Records, Alexandria, VA 22313-1450 or via the Internet.

In addition, information on the status of the application, including the mailing date of Office actions and the dates of receipt of correspondence filed in the Office, may also be accessed via the Internet through the Patent Electronic Business Center at www.uspto.gov using the public side of the Patent Application Information and Retrieval (PAIR) system. The direct link to access this status information is currently http://pair.uspto.gov/. Prior to publication, such status information is confidential and may only be obtained by applicant using the private side of PAIR.

Further assistance in electronically accessing the publication, or about PAIR, is available by calling the Patent Electronic Business Center at 1-866-217-9197.

Office of Data Managment, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

UNITED STATES PATENT AND TRADEMARK OFFICE

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APPLICATION NO.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/493,903	01/06/2015	8927606	2014-1250	7395

513 7590 12/17/2014

WENDEROTH, LIND & PONACK, L.L.P.
1030 15th Street, N.W.,
Suite 400 East
Washington, DC 20005-1503

ISSUE NOTIFICATION

The projected patent number and issue date are specified above.

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(application filed on or after May 29, 2000)

The Patent Term Adjustment is 0 day(s). Any patent to issue from the above-identified application will include an indication of the adjustment on the front page.

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (http://pair.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Application Assistance Unit (AAU) of the Office of Data Management (ODM) at (571)-272-4200.

APPLICANT(s) (Please see PAIR WEB site http://pair.uspto.gov for additional applicants):

Shirou SAWA, Hyogo, JAPAN;
SENJU PHARMACEUTICAL CO., LTD., Osaka, JAPAN, Assignee (with 37 CFR 1.172 Interest);
Shuhei FUJITA, Hyogo, JAPAN;

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: Mail Mail Stop ISSUE FEE
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
or Fax (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

513 7590 12/19/2014
WENDEROTH, LIND & PONACK, L.L.P.
1030 15th Street, N.W.,
Suite 400 East
Washington, DC 20005-1503

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission
I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

(Depositor's name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/493,903	09/23/2014	Shirou SAWA	2014-1250	7395

TITLE OF INVENTION: AQUEOUS LIQUID PREPARATION CONTAINING 2-AMINO-3-(4-BROMOBENZOYL)PHENYLACETIC ACID

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$960	$0	$0	$960	02/19/2015

EXAMINER	ART UNIT	CLASS-SUBCLASS
SOROUSH, LAYLA	1627	514-619000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).
- ☐ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.
- ☐ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 WENDEROTH, LIND & PONACK, L.L.P.
2
3

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE: SENJU PHARMACEUTICAL CO., LTD.

(B) RESIDENCE: (CITY and STATE OR COUNTRY): OSAKA, JAPAN

Please check the appropriate assignee category or categories (will not be printed on the patent): ☐ Individual ☒ Corporation or other private group entity ☐ Government

4a. The following fee(s) are submitted:
- ☒ Issue Fee
- ☐ Publication Fee (No small entity discount permitted)
- ☐ Advance Order - # of Copies .....

4b. Payment of Fee(s): **(Please first reapply any previously paid issue fee shown above)**
- ☐ A check is enclosed.
- ☒ Payment by credit card. ~~Form PTO-2038 is attached.~~
- ☒ The director is hereby authorized to charge the required fee(s), any deficiency, or credits any overpayment, to Deposit Account Number 23-0975 ..... (enclose an extra copy of this form).

5. **Change in Entity Status** (from status indicated above)
- ☐ Applicant certifying micro entity status. See 37 CFR 1.29
- ☐ Applicant asserting small entity status. See 37 CFR 1.27
- ☐ Applicant changing to regular undiscounted fee status.

NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.

NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.

NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31; see 37 CFR 1.4(d) for signature requirements and certifications.

Authorized Signature /Warren M. Cheek, Jr./ Digitally signed by Warren M. Cheek, Jr. DN: cn=Warren M. Cheek, Jr., o=, ou=, email=wcheek@wenderoth.com, c=US Date: 2014.11.21 13:01:08 -05'00' Date November 21, 2014

Typed or printed name Warren M. Cheek Registration No. 33,367

PTOL-85 Part B (10-13) Approved for use through 10/31/2013. OMB 0651-0033 U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Electronic Patent Application Fee Transmittal

Application Number:	14493903
Filing Date:	23-Sep-2014
Title of Invention:	AQUEOUS LIQUID PREPARATION CONTAINING 2-AMINO-3-(4-BROMOBENZOYL)PHENYLACETIC ACID
First Named Inventor/Applicant Name:	Shirou SAWA
Filer:	Warren M. Cheek Jr./Donna King
Attorney Docket Number:	2014-1250

Filed as Large Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Utility Appl Issue Fee	1501	1	960	960
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
			Total in USD ($)	**960**

Electronic Acknowledgement Receipt

EFS ID:	20766046
Application Number:	14493903
International Application Number:	
Confirmation Number:	7395
Title of Invention:	AQUEOUS LIQUID PREPARATION CONTAINING 2-AMINO-3-(4-BROMOBENZOYL)PHENYLACETIC ACID
First Named Inventor/Applicant Name:	Shirou SAWA
Customer Number:	513
Filer:	Warren M. Cheek Jr./maurice linder
Filer Authorized By:	Warren M. Cheek Jr.
Attorney Docket Number:	2014-1250
Receipt Date:	21-NOV-2014
Filing Date:	23-SEP-2014
Time Stamp:	14:19:12
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Credit Card
Payment was successfully received in RAM	$960
RAM confirmation Number	555
Deposit Account	230975
Authorized User	CHEEK JR., WARREN M.

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

Charge any Additional Fees required under 37 C.F.R. Section 1.16 (National application filing, search, and examination fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.17 (Patent application and reexamination processing fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.19 (Document supply fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.20 (Post Issuance fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.21 (Miscellaneous fees and charges)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Issue Fee Payment (PTO-85B)	AttachA_IF.pdf	415516 ddf1617e8025bf921e65a2b7ad88412e8af7c2d1	no	1

Warnings:

The PDF file has been signed with a digital signature and the legal effect of the document will be based on the contents of the file not the digital signature.

Information:

2	Fee Worksheet (SB06)	fee-info.pdf	30663 1363e483d9503e897c14300d4941ebc9a139c76f	no	2

Warnings:

Information:

Total Files Size (in bytes):	446179

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

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NOTICE OF ALLOWANCE AND FEE(S) DUE

513 7590 11/19/2014

WENDEROTH, LIND & PONACK, L.L.P.
1030 15th Street, N.W.,
Suite 400 East
Washington, DC 20005-1503

EXAMINER
SOROUSH, LAYLA

ART UNIT	PAPER NUMBER
1627	

DATE MAILED: 11/19/2014

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/493,903	09/23/2014	Shirou SAWA	2014-1250	7395

TITLE OF INVENTION: AQUEOUS LIQUID PREPARATION CONTAINING 2-AMINO-3-(4-BROMOBENZOYL)PHENYLACETIC ACID

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$960	$0	$0	$960	02/19/2015

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the ENTITY STATUS shown above. If the ENTITY STATUS is shown as SMALL or MICRO, verify whether entitlement to that entity status still applies.

If the ENTITY STATUS is the same as shown above, pay the TOTAL FEE(S) DUE shown above.

If the ENTITY STATUS is changed from that shown above, on PART B - FEE(S) TRANSMITTAL, complete section number 5 titled "Change in Entity Status (from status indicated above)".

For purposes of this notice, small entity fees are 1/2 the amount of undiscounted fees, and micro entity fees are 1/2 the amount of small entity fees.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Utility patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: Mail **Mail Stop ISSUE FEE**
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
or Fax (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

513 7590 11/19/2014
WENDEROTH, LIND & PONACK, L.L.P.
1030 15th Street, N.W.,
Suite 400 East
Washington, DC 20005-1503

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission
I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

(Depositor's name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/493,903	09/23/2014	Shirou SAWA	2014-1250	7395

TITLE OF INVENTION: AQUEOUS LIQUID PREPARATION CONTAINING 2-AMINO-3-(4-BROMOBENZOYL)PHENYLACETIC ACID

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$960	$0	$0	$960	02/19/2015

EXAMINER	ART UNIT	CLASS-SUBCLASS
SOROUSH, LAYLA	1627	514-619000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).
- ❑ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.
- ❑ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.
1 _____
2 _____
3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ❑ Individual ❑ Corporation or other private group entity ❑ Government

4a. The following fee(s) are submitted:
- ❑ Issue Fee
- ❑ Publication Fee (No small entity discount permitted)
- ❑ Advance Order - # of Copies _____

4b. Payment of Fee(s): **(Please first reapply any previously paid issue fee shown above)**
- ❑ A check is enclosed.
- ❑ Payment by credit card. Form PTO-2038 is attached.
- ❑ The director is hereby authorized to charge the required fee(s), any deficiency, or credits any overpayment, to Deposit Account Number _____ (enclose an extra copy of this form).

5. **Change in Entity Status** (from status indicated above)
- ❑ Applicant certifying micro entity status. See 37 CFR 1.29 — NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.
- ❑ Applicant asserting small entity status. See 37 CFR 1.27 — NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.
- ❑ Applicant changing to regular undiscounted fee status. — NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

PTOL-85 Part B (10-13) Approved for use through 10/31/2013. OMB 0651-0033 U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/493,903	09/23/2014	Shirou SAWA	2014-1250	7395

513 7590 11/19/2014

WENDEROTH, LIND & PONACK, L.L.P.
1030 15th Street, N.W.,
Suite 400 East
Washington, DC 20005-1503

EXAMINER	
SOROUSH, LAYLA	

ART UNIT	PAPER NUMBER
1627	

DATE MAILED: 11/19/2014

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(Applications filed on or after May 29, 2000)

The Office has discontinued providing a Patent Term Adjustment (PTA) calculation with the Notice of Allowance.

Section 1(h)(2) of the AIA Technical Corrections Act amended 35 U.S.C. 154(b)(3)(B)(i) to eliminate the requirement that the Office provide a patent term adjustment determination with the notice of allowance. See Revisions to Patent Term Adjustment, 78 Fed. Reg. 19416, 19417 (Apr. 1, 2013). Therefore, the Office is no longer providing an initial patent term adjustment determination with the notice of allowance. The Office will continue to provide a patent term adjustment determination with the Issue Notification Letter that is mailed to applicant approximately three weeks prior to the issue date of the patent, and will include the patent term adjustment on the patent. Any request for reconsideration of the patent term adjustment determination (or reinstatement of patent term adjustment) should follow the process outlined in 37 CFR 1.705.

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

OMB Clearance and PRA Burden Statement for PTOL-85 Part B

The Paperwork Reduction Act (PRA) of 1995 requires Federal agencies to obtain Office of Management and Budget approval before requesting most types of information from the public. When OMB approves an agency request to collect information from the public, OMB (i) provides a valid OMB Control Number and expiration date for the agency to display on the instrument that will be used to collect the information and (ii) requires the agency to inform the public about the OMB Control Number's legal significance in accordance with 5 CFR 1320.5(b).

The information collected by PTOL-85 Part B is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450. Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Notice of Allowability	Application No.	Applicant(s)	
	14/493,903	SAWA ET AL.	
	Examiner	Art Unit	
	LAYLA SOROUSH	1627	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *the T.D filed on 11/5/14, 11/06/14 and approved on 11/6/14 and 11/7/14*.

2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

3. ☒ The allowed claim(s) is/are *19-48*.

4. ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
   a) ☒ All b) ☐ Some* c) ☐ None of the:
      1. ☐ Certified copies of the priority documents have been received.
      2. ☒ Certified copies of the priority documents have been received in Application No. *10/525,006* .
      3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ A SUBSTITUTE OATH OR DECLARATION must be submitted. Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL PATENT APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient.

6. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   (a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review (PTO-948) attached
      1) ☐ hereto or 2) ☐ to Paper No./Mail Date _____.
   (b) ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

7. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
3. ☒ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date 10/16/14; 9/23/14
4. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
5. ☐ Notice of Informal Patent Application
6. ☒ Interview Summary (PTO-413), Paper No./Mail Date *10/22/14* .
7. ☒ Examiner's Amendment/Comment
8. ☒ Examiner's Statement of Reasons for Allowance
9. ☐ Other _____.

The present application is being examined under the pre-AIA first to invent provisions.

Acknowledgement of Receipt

Applicant's response filed on 11/05/2014 is acknowledged.

Claim Status

Claims 19-48 are pending.

Claims 19-48 are allowed.

Withdrawn Rejections

The Double Patenting rejections over U.S. Patent No. 8129431, 8497304, 8669290, 8754131, 8871813, US App. No. 14502014, 14269692 is withdrawn in view of the TD's filed on 11/05/2014 and 11/06/2014; and approved on 11/06/2014 and 11/07/2014.

Reasons for Allowance

The following is an examiner's statement of reasons for allowance:

The method as claimed are found to be patentable over the prior art because the prior art does not teach or fairly suggest a method for treating an inflammatory disease of an eye, the method comprising administering to said eye a stable aqueous liquid preparation that comprises: (a) a first component; and (b) a second component; wherein the first component is 2-amino-3-(4- bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof, wherein the hydrate is at least one selected from a 1/2 hydrate, 1 hydrate, and 3/2 hydrate; the first component is

the sole pharmaceutical active ingredient contained in the preparation; the second component is tyloxapol and is present in said liquid preparation in an amount sufficient to stabilize said first component; wherein said stable liquid preparation is formulated for ophthalmic administration; and wherein said liquid preparation is administered to said eye at a dose and a frequency effective to treat said inflammatory disease.

The closest prior arts of record, namely Chen et al. (US 6383471), teach a pharmaceutical composition including a hydrophobic therapeutic agent having at least one ionizable functional group, and a carrier. The carrier includes an ionizing agent capable of ionizing the functional group, a surfactant, and optionally solubilizers, triglycerides, and neutralizing agents (abstract). The reference teaches a hydrophobic therapeutic agent to include bromfenac (2-amino-3-(4-bromobenzoyl)phenalyacetic acid)(see claim 4). The hydrophobic therapeutic agent is used in less than about 1% by weight, and typically less than about 0.1% or 0.01% by weight (see col 4 lines 58-60) (renders obvious the limitation of claims 8 and 24). The reference further teaches surfactants inclusive of polyethylene glycol fatty acid esters and additionally teaches polyethylene glycol fatty acid monoesters such as peg-15 stearate, etc (see claims 21-22 24 and 27). The surfactants are selected from the group consisting of alcohols; polyoxyethylene alkylethers; fatty acids; glycerol fatty acid esters; acetylated glycerol fatty acid esters; lower alcohol fatty acids esters; polyethylene glycol fatty acids esters; polyethylene glycol glycerol fatty acid esters; polypropylene glycol fatty acid esters; polyoxyethylene glycerides; lactic acid derivatives of mono/diglycerides; propylene glycol diglycerides; sorbitan fatty acid esters; polyoxyethylene sorbitan fatty acid esters;

polyoxyethylene-polyoxypropylene block copolymers; transesterified vegetable oils; sterols; sterol derivatives; sugar esters; sugar ethers; sucroglycerides; polyoxyethylene vegetable oils; and polyoxyethylene hydrogenated vegetable oils. The pharmaceutical compositions of the present invention can be provided in the form of a solution preconcentrate; i.e., a composition as described above, and intended to be dispersed with water, either prior to administration, in the form of a drink, or dispersed in vivo (col 34 lines 63-68) (reads on an aqueous liquid preparation). The reference also teaches preservatives (see claim 64). Although formulations specifically suited to oral administration are presently preferred, the compositions of the present invention can also be formulated for topical, transdermal, ocular, pulmonary, vaginal, rectal, transmucosal or parenteral administration (col 35 lines 9-20). Chen et al. further teaches components that can be incorporated into the composition include inorganic acids inclusive of boric acid (col 46, line 6), solubilizer such as polyvinylpyrrolidone (claim 49), exemplifications of carriers comprising Edetate Disodium (col 4 table 20 formulations 65 and 66), and ionizing agents that deprotonate the acidic functional groups of the therapeutic agent are pharmaceutically acceptable organic or inorganic bases, inclusive of sodium hydroxide (col 11 lines 12-13) (reads on the limitations of claim 22).

However, Applicant presents excellent effects are clearly demonstrated by Experiments 1 to 3 of the present specification. Experiment 1 -- Stability of sodium 2-amino-3-(4-bromobenzoyl)phenyl acetate was evaluated. Namely, two eye drops of sodium 2-amino-3-(4-bromobenzoyl) phenylacetate comprising the components as

shown in Table 1 were prepared, filled respectively into a polypropylene container and subjected to a stability test at 60℃ for 4 weeks. As is apparent from Table 1, the stability test was carried out under the conditions of pH 7.0 at 60℃ for 4 weeks. Table 1 clearly shows that sodium 2-amino-3- (4-bromobenzoyl)phenylacetate in polyoxyl 40 stearate-containing preparation was more stable than that in polysorbate 80- containing preparation. As is apparent from Table 2, the remaining rate of sodium 2-amino-3-(4-bromobenzoyl)phenylacetate in the compositions A-07 and A-08 containing 0.02 w/v % and 0.05 w/v % of polyoxyl 40 stearate is not less than 90 % after storage at 60℃ for 4 weeks. Table 2 clearly shows that the compositions containing 0.02 w/v % and 0.05 w/v % of polyoxyl 40 stearate have sufficient stability for eye drops.

The method as claimed are found to be patentable over the prior art because the prior art does not teach or fairly suggest a method for treating an inflammatory disease of an eye, the method comprising administering to said eye a stable aqueous liquid preparation that comprises: (a) a first component; and (b) a second component; wherein the first component is 2-amino-3-(4- bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof, wherein the hydrate is at least one selected from a 1/2 hydrate, 1 hydrate, and 3/2 hydrate; the first component is the sole pharmaceutical active ingredient contained in the preparation; the second component is tyloxapol and is present in said liquid preparation in an amount sufficient to stabilize said first component; wherein said stable liquid preparation is formulated for ophthalmic administration; and wherein said liquid preparation is administered to said eye at a dose and a frequency effective to treat said inflammatory disease.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled “Comments on Statement of Reasons for Allowance.”

Any inquiry concerning this communication or earlier communications from the examiner should be directed to LAYLA SOROUSH whose telephone number is (571)272-5008. The examiner can normally be reached on 8:30a.m.-5:00p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner’s supervisor, Sreenivasan Padmanabhan can be reached on (571)272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Layla Soroush/

Examiner, Art Unit 1627

Examiner-Initiated Interview Summary	Application No.	Applicant(s)	
	14/493,903	SAWA ET AL.	
	Examiner	Art Unit	
	LAYLA SOROUSH	1627	

All participants (applicant, applicant's representative, PTO personnel):

(1) *LAYLA SOROUSH*. (3)_____.

(2) *Warren Cheek*. (4)_____.

Date of Interview: *22 October 2014*.

Type: ☒ Telephonic ☐ Video Conference
☐ Personal [copy given to: ☐ applicant ☐ applicant's representative]

Exhibit shown or demonstration conducted: ☐ Yes ☐ No.
If Yes, brief description: _____.

Issues Discussed ☐101 ☐112 ☐102 ☐103 ☐Others
(For each of the checked box(es) above, please describe below the issue and detailed description of the discussion)

Claim(s) discussed: _____.

Identification of prior art discussed: _____.

Substance of Interview
(For each issue discussed, provide a detailed description and indicate if agreement was reached. Some topics may include: identification or clarification of a reference or a portion thereof, claim interpretation, proposed amendments, arguments of any applied references etc...)

In the interest of compact prosecution, a proposal was made to the Applicant to overcome the remaining issues and proceed to allowance. Applicant agreed and gave the Examiner authorization to make the appropriate claim amendments in an Examiner's Amendment .

Applicant recordation instructions: It is not necessary for applicant to provide a separate record of the substance of interview.

Examiner recordation instructions: Examiners must summarize the substance of any interview of record. A complete and proper recordation of the substance of an interview should include the items listed in MPEP 713.04 for complete and proper recordation including the identification of the general thrust of each argument or issue discussed, a general indication of any other pertinent matters discussed regarding patentability and the general results or outcome of the interview, to include an indication as to whether or not agreement was reached on the issues raised.

☐ Attachment

INFORMATION DISCLOSURE STATEMENT

FORM PTO/SB/08 A&B (*modified*)

U.S. DEPARTMENT OF COMMERCE
PATENT AND TRADEMARK OFFICE

LIST OF REFERENCES CITED BY APPLICANT(S)
(*Use several sheets if necessary*)

Date Submitted to PTO: September 23, 2014

ATTY DOCKET NO. 2014-1250	**SERIAL NO.** NEW
FIRST NAMED INVENTOR Shirou SAWA	
FILING DATE September 23, 2014	**GROUP**

U.S. PATENT DOCUMENTS

*EXAMINER INITIAL		DOCUMENT NUMBER	DATE	NAME	CLASS	SUBCLASS	FILING DATE IF APPROPRIATE
/L.S./	AA	5,603,929	2/1997	Desai et al.			
	AB	5,653,972	8/1997	Desai et al.			
	AC	4,910,225	3/1990	Ogawa et al.			
	AD	5,110,493	5/1992	Cherng-Chyi et al.			
	AE	6,383,471	5/2002	Chen et al.			
	AF	4,045,576	8/1977	Welstead, Jr. et al.			
	AG	4,683,242	7/1987	Poser			
	AH	6,319,513	11/2001	Dobrozsi			
	AI	2007/0082857	4/2007	Sawa			
	AJ	6,369,112	4/2002	Xia			
	AK	5,998,465	12/1999	Hellberg et al.			
	AL	5,597,560	1/1997	Bergamini et al.			
	AM	6,395,746	5/2002	Cagle et al.			
	AN	5,475,034	12/1995	Yanni et al.			
	AO	5,540,930	7/1996	Guy			
	AP	5,942,508	8/1999	Sawa			
	AQ	6,274,592	8/2001	Sawa			
	AR	2001/0056098	12/2001	Sawa			
	AS	6,274,609	8/2001	Yasueda et al.			
	AT	5,558,876	9/1996	Desai et al.			
	AU	6,162,393	12/2000	De Bruiju et al.			
	AV	8,129,431	3/2012	Sawa et al.			
	AW	6,107,343	8/2000	Sallmann et al.			
	AX	2,880,130	3/1959	Johnson			

EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609; draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

INFORMATION DISCLOSURE STATEMENT

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Date Submitted to PTO: September 23, 2014

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2014-1250	NEW
FIRST NAMED INVENTOR	
Shirou SAWA	
FILING DATE	**GROUP**
September 23, 2014	

/L.S./	AY	2,880,138	3/1959	Johnson				
/L.S./	AZ	6,071,904	6/2000	Ali et al.				

FOREIGN PATENT DOCUMENTS

		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION/ADDITIONAL INFORMATIOJN YES	NO
/L.S./	BA	9-503791	4/1997	JP				
	BB	2-124819	5/1990	JP				
	BC	1-104023	4/1989	JP				
	BD	00/59475	10/2000	WO				
	BE	11-228404	8/1999	JP			Yes	
	BF	5-223052	8/1993	JP			Abstract	
	BG	62-126124	6/1987	JP				No
	BH	96/14829	5/1996	WO				
	BI	01/15677	3/2001	WO				
	BJ	2 013 188	9/1990	CA				
	BK	02/13804	2/2002	WO				
	BL	707 119	9/1995	AU				
	BM	02083323	3/1990	JP				
	BN	2002-308764	10/2002	JP				
	BO	0 306 984	3/1989	EP				
	BP	22042/88	3/1989	AU				
	BQ	94/15597	7/1994	WO				
	BR	2 383 971	3/2001	CA				
	BS	0 274 870	7/1988	EP				
	BT	94/05298	3/1994	WO				

OTHER DOCUMENT(S) *(Including Author, Title, Date, Pertinent Pages, Etc.)*

/L.S./	CA	New Drugs in Japan, 2001, 2001 Edition, Published by Yakuji Nippo Ltd., May 11, 2001, pp. 27-29, and its English translation of the material portions.

Examiner Initial if reference considered, whether or not citation is in conformance with MPEP 609; draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

Sheet 3 of 5		INFORMATION DISCLOSURE STATEMENT	
FORM PTO/SB/08 A&B (*modified*) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE LIST OF REFERENCES CITED BY APPLICANT(S) (*Use several sheets if necessary*) Date Submitted to PTO: September 23, 2014		**ATTY DOCKET NO.** 2014-1250	**SERIAL NO.** NEW
		FIRST NAMED INVENTOR Shirou SAWA	
		FILING DATE September 23, 2014	**GROUP**

/L.S./	CB	ISTA Pharmaceuticals, "New Drug Applications: Xibrom", http://www.drugs.com/nda/xibrom_040525.htmt, accessed online 9/19/2007.
	CC	Nolan et al., "The Topical Anti-Inflammatory and Analgesic Properties of Bromfenic in Rodents", Agents and Actions, Vol. 25, No. 1-2, pp. 77-85, August 1988.
	CD	Corrected partial English translation of New Drugs in Japan, 2001, 2001 Edition, Published by Yakuji Nippo Ltd., May 11, 2001, pp. 27-29, previously submitted on April 11, 2005.
	CE	Complete English translation of New Drugs in Japan, 2001, 2001 Edition, Published by Yakuji Nippo Ltd., May 11, 2001, pp. 27-29.
	CF	Notice of Opposition dated February 19, 2009 issued by EPO in connection with the corresponding European patent application and Opposition.
	CG	http://medical-dictionary.thefreedictionary.com/prophylactic accessed 12/15/2009.
	CH	Y. Hara, "Evaluation of New Drugs by Clinicians", Clinics & Drug Therapy, Vol. 19, No. 10, October 2000, pp. 1-2.
	CI	G. Smolin, M.D., "New Drugs in Ophthalmology", International Ophthalmology Clinics, Vol. 36, No. 2, 1996, pp. 1-9.
	CJ	ISTA News Release, XIBROM™, Bromfenac Ophthalmic Solution, 2007, p.1.
	CK	S. Prince et al., "Analysis of Benzalkonium Chloride and its Homologs: HPLC Versus HPCE[1]", Journal of Pharmaceutical and Biomedical Analysis, Vol. 19, pp. 877-882, 1999.
	CL	M. Doughty, "Therapeutics: Medicines Update *p18* Side-Effects of Anti-Epilepsy Drugs", Optician, Vol. 223, No. 5853, May 31, 2002, pp. 16-22.
	CM	I. Reddy, Ph.D., "Ocular Therapeutics and Drug Delivery", Technomics Publishing Co., Basel, pp. 42-43, 390, 1996.
	CN	H. Schott, "Comparing the Surface Chemical Properties and the Effect of Salts on the Cloud Point of a Conventional Nonionic Surfactant, Octoxynol 9 (Triton X-100), and of its Oligomer, Tyloxapol (Triton WR-1339)", Journal of Colloid and Interface Science, Vol. 205, pp. 496-502, 1998.
	CO	O. Regev, "Aggregation Behavior of Tyloxapol, a Nonionic Surfactant Oligomer, in Aqueous Solution", Journal of Colloid and Interface Science, Vol. 210, pp. 8-17, 1999.
	CP	PDR 50th Edition 1996, Physicans' Desk Reference, p. 469.
	CQ	PDR 54th Edition 2000, Physicans' Desk Reference, pp. 486-487, 491-492.
	CR	V. A. Ostrovskii et al., "Acid-Base Properties of 5-Substituted Tetrazoles", Khimiya Get. Soc., pp. 412-416, 1981.
	CS	LOTEMAX™ product brochure, Loteprednol Etabonate Ophthalmic Suspension, 0.5%, pp. 1-16, March 6, 1998.

EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609; draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

INFORMATION DISCLOSURE STATEMENT

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PATENT AND TRADEMARK OFFICE

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Date Submitted to PTO: September 23, 2014

ATTY DOCKET NO.	SERIAL NO.
2014-1250	NEW
FIRST NAMED INVENTOR Shirou SAWA	
FILING DATE September 23, 2014	**GROUP**

/L.S./	CT	Webester's New World Dictionary of the American Language, Second College Edition, "monohydrate", Simon & Schuster, NY, p. 920, 1982.
	CU	Pharmacopeia, R. S. Cook et al., "Edetic Acid", pp. 177-179, JT Steward, "Sodium Metabisulfide", pp. 451-453, 2000.
	CV	Yakuji Nippo Limited, "Recent New Drugs 2001", Japanese Pharmacopoeia 2001 Edition, pp. 27-29, May 2001 (English translation).
	CW	Sigma-Aldrich catalog, Biochemicals and Reagents for Life Science Research, p. 175, 2000.
	CX	G. Patani et al., "Bioisosterism: A Rational Approach in Drug Design", Chemical Reviews, Vol. 96, No. 8, pp. 3147-3176, 1996.
	CY	P. Deluca et al., "Interaction of Preservatives with Macromolecules IV, Binding of Quaternary Ammonium Compounds by Nonionic Agents", Journal of the American Pharmaceutical Association, Vol. 49, No. 7, pp. 430-437, July 1960.
	CZ	D. Guttman et al., "Solubilization of Anti-Inflammatory Steroids by Aqueous Solutions of Triton WR-1339", Journal of Pharmaceutical Sciences, Vol. 50, No. 4, pp. 305-307, April 1961.
	CCA	T. Fan et al., "Determination of Benzalkonium Chloride in Ophthalmic Solutions Containing Tyloxapol by Solid-Phase Extraction and Reversed-Phase High-Performance Liquid Chromatography", Journal of Pharmaceutical Sciences, Vol. 82, No. 11, pp. 1172-1174, November 1993.
	CCB	FDA Website search of Orange Book (Patent and Exclusivity Search Results): Approved Drug Products with Therapeutic Equivalence Evaluations; Search Results for N203168, 2014.
	CCC	FDA website search of Orange Book (Detail Record Search): Approved Drug Products with Therapeutic Equivalence Evaluations, Search Results for N203168, 2014.
	CCD	Remington: The Science and Practice of Pharmacy, 20th Edition, "Boric Acid", Lippincoh, Williams, Baltimore MD, p. 1041, 2000.
	CCE	PDR 52nd Edition 1998, Physicans' Desk Reference, "Duract", Method Economics Co., Montrale, NJ, pp. 3035-3037.
	CCF	ALREX™ product package, Loteprednol Etabonate, Ophthalmic Suspension, 0.2%, pp. 1-13, 1998.
	CCG	XIBROM™ product package, Bromfenac Ophthalmic Solution, 0.09%, pp. 3-6, 2000.
	CCH	BROMDAY product package, Bromfenac Ophthalmic Solution, 0.09%, pp. 4-8, 1997.
	CCI	PROLENSA™ product package, Bromfenac Ophthalmic Solution, 0.07%, pp. 4-9, 2013.
	CCJ	PDR 54 Edition 2000, Physicans' Desk Reference, pp. 489-491, TOBRADEX®, Tobramycin and Dexamethasone Ophthalmic Suspension and Ointment.
	CCK	FDA website description of VOLTAREN, Diclofenac Sodium, Ophthalmic Solution, 0.1%, pp. 1-2, 1991.

EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609; draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

Sheet 5 of 5		INFORMATION DISCLOSURE STATEMENT	
FORM PTO/SB/08 A&B (*modified*) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE LIST OF REFERENCES CITED BY APPLICANT(S) (*Use several sheets if necessary*) Date Submitted to PTO: September 23, 2014		**ATTY DOCKET NO.** 2014-1250	**SERIAL NO.** NEW
		FIRST NAMED INVENTOR Shirou SAWA	
		FILING DATE September 23, 2014	**GROUP**

/L.S./	CCL	ALREX™ product package, Loteprednol Etabonate, Ophthalmic Suspension, 0.2%, pp. 1-13, 1998.
	CCM	The United States Pharmacopeia, The National Formulary, USP 24, NF 19, pp. 1809-1813, 1864-1866, 2000.
	CCN	Dorset & Baber, Webster's New Twentieth Century Dictionary, Second Edition, "Ophthalmic" and "Ophthalmitic" p. 1254, 1979.
	CCO	BRONUCK® news release, Bromfenac Sodium Hydrate Ophthalmic Solution, p.1, 2005.

EXAMINER	/Layla Soroush/	DATE CONSIDERED

EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609; draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

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Alexandria, Virginia 22313-1450
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BIB DATA SHEET

CONFIRMATION NO. 7395

SERIAL NUMBER	FILING or 371(c) DATE RULE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
14/493,903	09/23/2014	514	1627	2014-1250

APPLICANTS

SENJU PHARMACEUTICAL CO., LTD., Osaka, JAPAN, Assignee (with 37 CFR 1.172 Interest);

INVENTORS

Shirou SAWA, Hyogo, JAPAN;
Shuhei FUJITA, Hyogo, JAPAN;

**** CONTINUING DATA ***************************

This application is a DIV of 14/261,720 04/25/2014 PAT 8871813
which is a DIV of 14/165,976 01/28/2014 PAT 8754131
which is a DIV of 13/687,242 11/28/2012 PAT 8669290
which is a DIV of 13/353,653 01/19/2012 PAT 8497304
which is a DIV of 10/525,006 03/28/2005 PAT 8129431
which is a 371 of PCT/JP2004/000350 01/16/2004

**** FOREIGN APPLICATIONS ***************************

JAPAN 2003-012427 01/21/2003

**** IF REQUIRED, FOREIGN FILING LICENSE GRANTED ****

09/29/2014

Foreign Priority claimed	35 USC 119(a-d) conditions met	Verified and Acknowledged	Met after Allowance	STATE OR COUNTRY	SHEETS DRAWINGS	TOTAL CLAIMS	INDEPENDENT CLAIMS
☑ Yes ☐ No	☑ Yes ☐ No	/LAYLA SOROUSH/ Examiner's Signature	☑ LS Initials	JAPAN	0	30	3

ADDRESS

WENDEROTH, LIND & PONACK, L.L.P.
1030 15th Street, N.W.,
Suite 400 East
Washington, DC 20005-1503
UNITED STATES

TITLE

AQUEOUS LIQUID PREPARATION CONTAINING 2-AMINO-3-(4-BROMOBENZOYL)PHENYLACETIC ACID

FILING FEE RECEIVED		
2400	FEES: Authority has been given in Paper No._____ to charge/credit DEPOSIT ACCOUNT No._____ for following:	☐ All Fees ☐ 1.16 Fees (Filing) ☐ 1.17 Fees (Processing Ext. of time) ☐ 1.18 Fees (Issue) ☐ Other _____ ☐ Credit

Search Notes	Application/Control No.	Applicant(s)/Patent under Reexamination	
	14/493,903	SAWA ET AL.	
	Examiner	Art Unit	
	LAYLA SOROUSH	1627	

SEARCHED			
Class	Subclass	Date	Examiner
514	619	10/22/14	LS
514	535	10/22/14	LS
514	570	10/22/14	LS

INTERFERENCE SEARCHED			
Class	Subclass	Date	Examiner
514	**618**	**10/22/14**	**LS**

SEARCH NOTES (INCLUDING SEARCH STRATEGY)		
	DATE	EXMR
STIC (see also 13535653); and updated npl and EAST	10/22/14	LS
odp:SAWA, SHIROU and FUJITA, SHUHEI	10/22/14	LS

Issue Classification	Application/Control No. 14/493,903	Applicant(s)/Patent under Reexamination SAWA ET AL.
	Examiner LAYLA SOROUSH	Art Unit 1627

ISSUE CLASSIFICATION

ORIGINAL		INTERNATIONAL CLASSIFICATION											
CLASS	SUBCLASS	CLAIMED						NON-CLAIMED					
514	619	A	1	N	37	/18							/
CROSS REFERENCES		A	61	K	31	/165							/
CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)												
514	535 570 618	A	1	N	37	/44							/
		A	61	K	31	/24							/
		A	1	N	37	/10							/
		A	61	K	31	/19							/
						/							/

(Assistant Examiner) (Date)	/Layla Soroush/ 11/7/14	Total Claims Allowed: 30	
(Legal Instruments Examiner) (Date)	(Primary Examiner) (Date)	O.G. Print Claim(s) 1	O.G. Print Fig. NONE

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original
	1	13	31		61		91		121		151		181
	2	14	32		62		92		122		152		182
	3	15	33		63		93		123		153		183
	4	16	34		64		94		124		154		184
	5	17	35		65		95		125		155		185
	6	18	36		66		96		126		156		186
	7	19	37		67		97		127		157		187
	8	20	38		68		98		128		158		188
	9	21	39		69		99		129		159		189
	10	22	40		70		100		130		160		190
	11	23	41		71		101		131		161		191
	12	24	42		72		102		132		162		192
	13	25	43		73		103		133		163		193
	14	26	44		74		104		134		164		194
	15	27	45		75		105		135		165		195
	16	28	46		76		106		136		166		196
	17	29	47		77		107		137		167		197
	18	30	48		78		108		138		168		198
1	19		49		79		109		139		169		199
2	20		50		80		110		140		170		200
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4	22		52		82		112		142		172		202
5	23		53		83		113		143		173		203
6	24		54		84		114		144		174		204
7	25		55		85		115		145		175		205
8	26		56		86		116		146		176		206
9	27		57		87		117		147		177		207
10	28		58		88		118		148		178		208
11	29		59		89		119		149		179		209
12	30		60		90		120		150		180		210

Sheet 1 of 3

INFORMATION DISCLOSURE STATEMENT

FORM PTO/SB/08 A&B (*modified*)

U.S. DEPARTMENT OF COMMERCE
PATENT AND TRADEMARK OFFICE

LIST OF REFERENCES CITED BY APPLICANT(S)
(*Use several sheets if necessary*)

Date Submitted to PTO: October 16, 2014

ATTY DOCKET NO.	**SERIAL NO.**
2014-1250	14/493,903
FIRST NAMED INVENTOR	
Shirou SAWA	
FILING DATE	**GROUP**
September 23, 2014	

U.S. PATENT DOCUMENTS

*EXAMINER INITIAL		DOCUMENT NUMBER	DATE	NAME	CLASS	SUBCLASS	FILING DATE IF APPROPRIATE
/L.S./	AA	8,129,431	3/2012	Sawa et al.			
	AB	6,107,343	8/2000	Sallmann et al.			
	AC	4,910,225	3/1990	Ogawa et al.			
	AD	5,603,929	2/1997	Desai et al.			
	AE	5,475,034	12/1995	Yanni et al.			
	AF	5,558,876	9/1996	Desai et al.			
	AG	6,274,609	8/2001	Yasueda et al.			
	AH	5,540,930	7/1996	Guy et al.			
	AI	2,880,130	3/1959	Johnson			
	AJ	2,880,138	3/1959	Johnson			
	AK	6,071,904	6/2000	Ali et al.			
	AL	5,597,560	1/1997	Bergamini et al.			

FOREIGN PATENT DOCUMENTS

		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION/ADDITIONAL INFORMATION YES	NO
/L.S./	BA	2 013 188	9/1990	CA				
	BB	22042/88	3/1989	AU				
	BC	94/15597	7/1994	WO				
	BD	2 383 971	3/2001	CA				
	BE	02/13804	2/2002	WO				
	BF	0 274 870	7/1988	EP				
	BG	94/05298	3/1994	WO				

OTHER DOCUMENT(S) *(Including Author, Title, Date, Pertinent Pages, Etc.)*

/L.S./	CA	Y. Hara, "Evaluation of New Drugs by Clinicians", Clinics & Drug Therapy, Vol. 19, No. 10, October 2000, pp. 1-2.
/L.S./	CB	G. Smolin, M.D., "New Drugs in Ophthalmology", International Ophthalmology Clinics, Vol. 36, No. 2, 1996, pp. 1-9.

Examiner Initial if reference considered, whether or not citation is in conformance with MPEP 609; draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

INFORMATION DISCLOSURE STATEMENT

FORM PTO/SB/08 A&B (*modified*)

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PATENT AND TRADEMARK OFFICE

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(*Use several sheets if necessary*)

Date Submitted to PTO: October 16, 2014

ATTY DOCKET NO.	SERIAL NO.
2014-1250	14/493,903
FIRST NAMED INVENTOR Shirou SAWA	
FILING DATE September 23, 2014	**GROUP**

/L.S./	CC	ISTA News Release, XIBROM™, Bromfenac Ophthalmic Solution, 2007, p.1.
	CD	S. Prince et al., "Analysis of Benzalkonium Chloride and its Homologs: HPLC Versus HPCE[1]", Journal of Pharmaceutical and Biomedical Analysis, Vol. 19, pp. 877-882, 1999.
	CE	M. Doughty, "Therapeutics: Medicines Update *p18* Side-Effects of Anti-Epilepsy Drugs", Optician, Vol. 223, No. 5853, May 31, 2002, pp. 16-22.
	CF	I. Reddy, Ph.D., "Ocular Therapeutics and Drug Delivery", Technomics Publishing Co., Basel, pp. 42-43, 390, 1996.
	CG	H. Schott, "Comparing the Surface Chemical Properties and the Effect of Salts on the Cloud Point of a Conventional Nonionic Surfactant, Octoxynol 9 (Triton X-100), and of its Oligomer, Tyloxapol (Triton WR-1339)", Journal of Colloid and Interface Science, Vol. 205, pp. 496-502, 1998.
	CH	O. Regev, "Aggregation Behavior of Tyloxapol, a Nonionic Surfactant Oligomer, in Aqueous Solution", Journal of Colloid and Interface Science, Vol. 210, pp. 8-17, 1999.
	CI	PDR 50th Edition 1996, Physicans' Desk Reference, p. 469.
	CJ	PDR 54th Edition 2000, Physicans' Desk Reference, pp. 486-487, 491-492.
	CK	V. A. Ostrovskii et al., "Acid-Base Properties of 5-Substituted Tetrazoles", Khimiya Get. Soc., pp. 412-416, 1981.
	CL	LOTEMAX™ product brochure, Loteprednol Etabonate Ophthalmic Suspension, 0.5%, pp. 1-16, March 6, 1998.
	CM	Webester's New World Dictionary of the American Language, Second College Edition, "monohydrate", Simon & Schuster, NY, p. 920, 1982.
	CN	Pharmacopeia, R. S. Cook et al., "Edetic Acid", pp. 177-179, JT Steward, "Sodium Metabisulfide", pp. 451-453, 2000.
	CO	Yakuji Nippo Limited, "Recent New Drugs 2001", Japanese Pharmacopoeia 2001 Edition, pp. 27-29, May 2001 (English translation).
	CP	Sigma-Aldrich catalog, Biochemicals and Reagents for Life Science Research, p. 175, 2000.
	CQ	G. Patani et al., "Bioisosterism: A Rational Approach in Drug Design", Chemical Reviews, Vol. 96, No. 8, pp. 3147-3176, 1996.
	CR	P. Deluca et al., "Interaction of Preservatives with Macromolecules IV, Binding of Quaternary Ammonium Compounds by Nonionic Agents", Journal of the American Pharmaceutical Association, Vol. 49, No. 7, pp. 430-437, July 1960.
	CS	D. Guttman et al., "Solubilization of Anti-Inflammatory Steroids by Aqueous Solutions of Triton WR-1339", Journal of Pharmaceutical Sciences, Vol. 50, No. 4, pp. 305-307, April 1961.
	CT	T. Fan et al., "Determination of Benzalkonium Chloride in Ophthalmic Solutions Containing Tyloxapol by Solid-Phase Extraction and Reversed-Phase High-Performance Liquid Chromatography", Journal of Pharmaceutical Sciences, Vol. 82, No. 11, pp. 1172-1174, November 1993.

EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609; draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

INFORMATION DISCLOSURE STATEMENT

FORM PTO/SB/08 A&B (*modified*) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE LIST OF REFERENCES CITED BY APPLICANT(S) (*Use several sheets if necessary*) Date Submitted to PTO: October 16, 2014	**ATTY DOCKET NO.** 2014-1250	**SERIAL NO.** 14/493,903
	FIRST NAMED INVENTOR Shirou SAWA	
	FILING DATE September 23, 2014	**GROUP**

/L.S./	CU	FDA Website search of Orange Book (Patent and Exclusivity Search Results): Approved Drug Products with Therapeutic Equivalence Evaluations; Search Results for N203168, 2014.
	CV	FDA website search of Orange Book (Detail Record Search): Approved Drug Products with Therapeutic Equivalence Evaluations, Search Results for N203168, 2014.
	CW	Remington: The Science and Practice of Pharmacy, 20th Edition, "Boric Acid", Lippincoh, Williams, Baltimore MD, p. 1041, 2000.
	CX	PDR 52nd Edition 1998, Physicans' Desk Reference, "Duract", Method Economics Co., Montrale, NJ, pp. 3035-3037.
	CY	ALREX™ product package, Loteprednol Etabonate, Ophthalmic Suspension, 0.2%, pp. 1-13, 1998.
	CZ	XIBROM™ product package, Bromfenac Ophthalmic Solution, 0.09%, pp. 3-6, 2000.
	CAA	BROMDAY product package, Bromfenac Ophthalmic Solution, 0.09%, pp. 4-8, 1997.
	CAB	PROLENSA™ product package, Bromfenac Ophthalmic Solution, 0.07%, pp. 4-9, 2013.
	CAC	PDR 54 Edition 2000, Physicans' Desk Reference, pp. 489-491, TOBRADEX®, Tobramycin and Dexamethasone Ophthalmic Suspension and Ointment.
	CAD	FDA website description of VOLTAREN, Diclofenac Sodium, Ophthalmic Solution, 0.1%, pp. 1-2, 1991.
	CAE	The United States Pharmacopeia, The National Formulary, USP 24, NF 19, pp. 1809-1813, 1864-1866, 2000.
	CAF	Dorset & Baber, Webster's New Twentieth Century Dictionary, Second Edition, "Ophthalmic" and "Ophthalmitic" p. 1254, 1979.
	CAG	BRONUCK® news release, Bromfenac Sodium Hydrate Ophthalmic Solution, p.1, 2005.
	CAH	Petition for *Inter Partes* Review of USP 8,669,290 to Sawa et al., Metrics, Inc. v. Senju Pharmaceutical Co., Ltd, pp. 1-71.
↓	CAI	Petition for *Inter Partes* Review of USP 8,129,431 to Sawa et al., Metrics, Inc. v. Senju Pharmaceutical Co., Ltd, pp. 1-71.

EXAMINER	/Layla Soroush/	DATE CONSIDERED	

EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609; draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

Application Number	Application/Control No.	Applicant(s)/Patent under Reexamination	
	14/493,903	SAWA ET AL.	

Document Code - DISQ	Internal Document – DO NOT MAIL

TERMINAL DISCLAIMER	☒ APPROVED	☐ DISAPPROVED
Date Filed : 11/6/14	**This patent is subject to a Terminal Disclaimer**	

Approved/Disapproved by:

Janice Ford

U.S. Patent and Trademark Office

Application Number	Application/Control No.	Applicant(s)/Patent under Reexamination	
	14/493,903	SAWA ET AL.	

Document Code - DISQ	Internal Document – DO NOT MAIL

TERMINAL DISCLAIMER	☒ APPROVED	☐ DISAPPROVED
Date Filed : 05 NOV 2014	**This patent is subject to a Terminal Disclaimer**	

Approved/Disapproved by:

Six TDs filed and approved.

JAB

U.S. Patent and Trademark Office

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Named Inventor	:	Attorney Docket No. 2014-1250
Shirou SAWA	:	**Confirmation No. 7395**
Serial No. 14/493,903	:	Group Art Unit **Not Yet Assigned**
Filed September 23, 2014	:	Examiner **Not Yet Assigned**
AQUEOUS LIQUID PREPARATION CONTAINING 2-AMINO-3-(4-BROMOBENZOYL)PHENYLACETIC ACID	:	**Mail Stop: AMENDMENT**

RESPONSE

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir/Madam:

In response to the Examiner's request, we are enclosing herewith one additional Terminal Disclaimer to overcome the double patenting rejection over the claims for the above-identified application.

Respectfully submitted,

/Warren M. Cheek, Jr./

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Attorney for Applicant

WMC/dlk
Washington, D.C. 20005-1503
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Facsimile (202) 721-8250
November 6, 2014

The USPTO is hereby authorized to charge any fees under 37 C.F.R. §§ 1.16, 1.17, and 1.492, which may be required by this paper to Deposit Account No. 23-0975.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Named Inventor	:	Attorney Docket No. 2014-1250
Shirou SAWA	:	**Confirmation No. 7395**
Serial No. 14/493,903	:	Group Art Unit **Not Yet Assigned**
Filed September 23, 2014	:	Examiner **Not Yet Assigned**
AQUEOUS LIQUID PREPARATION CONTAINING 2-AMINO-3-(4-BROMOBENZOYL)PHENYLACETIC ACID	:	**Mail Stop: AMENDMENT**

TERMINAL DISCLAIMER UNDER 37 CFR 1.321

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir/Madam:

The owner, SENJU PHARMACEUTICAL CO., LTD., of 100% interest in the instant application, hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application, which would extend beyond the expiration date of the full statutory term defined in 35 USC 154 and 173, as shortened by any terminal disclaimer, of prior Patent No. 8,669,290, issued March 11, 2014. The owner hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and the prior patent are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors or assigns.

In making the above disclaimer, the owner does not disclaim the terminal part of any patent granted on the instant application that would extend to the expiration date of the full statutory term as defined in 35 USC 154 and 173 of the prior patent, as presently shortened by any terminal disclaimer, in the event that it later: expires for failure to pay a maintenance fee; is held unenforceable; is found invalid by a court of competent jurisdiction; is statutorily disclaimed in whole or terminally disclaimed under 37 CFR 1.321; has all claims cancelled by a

reexamination certificate; is reissued; or is in any manner terminated prior to the expiration of its full statutory term as presently shortened by any terminal disclaimer.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

[X] The undersigned is empowered to act on behalf of the organization.

[] The undersigned is an attorney of record.

/Warren M. Cheek, Jr./

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Date: 2014.11.06 15:24:01 -05'00'

November 6, 2014

Warren M. Cheek
Reg. No. 33,367

Terminal disclaimer fee under 37 CFR 1.20(d) is included.

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Telephone (202) 721-8200
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Electronic Patent Application Fee Transmittal

Application Number:	14493903
Filing Date:	23-Sep-2014
Title of Invention:	AQUEOUS LIQUID PREPARATION CONTAINING 2-AMINO-3-(4-BROMOBENZOYL)PHENYLACETIC ACID
First Named Inventor/Applicant Name:	Shirou SAWA
Filer:	Warren M. Cheek Jr./Donna King
Attorney Docket Number:	2014-1250

Filed as Large Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
Statutory or Terminal Disclaimer	1814	1	160	160
		Total in USD ($)		**160**

Electronic Acknowledgement Receipt

EFS ID:	20627550
Application Number:	14493903
International Application Number:	
Confirmation Number:	7395
Title of Invention:	AQUEOUS LIQUID PREPARATION CONTAINING 2-AMINO-3-(4-BROMOBENZOYL)PHENYLACETIC ACID
First Named Inventor/Applicant Name:	Shirou SAWA
Customer Number:	513
Filer:	Warren M. Cheek Jr./maurice linder
Filer Authorized By:	Warren M. Cheek Jr.
Attorney Docket Number:	2014-1250
Receipt Date:	06-NOV-2014
Filing Date:	23-SEP-2014
Time Stamp:	15:54:15
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Credit Card
Payment was successfully received in RAM	$160
RAM confirmation Number	2350
Deposit Account	230975
Authorized User	CHEEK JR., WARREN M.

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

Charge any Additional Fees required under 37 C.F.R. Section 1.16 (National application filing, search, and examination fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.17 (Patent application and reexamination processing fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.19 (Document supply fees)

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File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Supplemental Response or Supplemental Amendment	AttachA_Response.pdf	173109 18dbd52236f1315064aa8ecf3aeb23cd3aa65ccf	no	1
Warnings:					
The PDF file has been signed with a digital signature and the legal effect of the document will be based on the contents of the file not the digital signature.					
Information:					
2	Terminal Disclaimer Filed	AttachB_TD.pdf	180139 1245809a9c91d4c7134a9bdd6c1e8b70059cd9f0	no	2
Warnings:					
The PDF file has been signed with a digital signature and the legal effect of the document will be based on the contents of the file not the digital signature.					
Information:					
3	Fee Worksheet (SB06)	fee-info.pdf	30859 8f4f76fa40bd50bf910448aa52629cf0e9e0887f	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	384107		

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New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Named Inventor	:	Attorney Docket No. 2014-1250
Shirou SAWA	:	**Confirmation No. 7395**
Serial No. 14/493,903	:	Group Art Unit **Not Yet Assigned**
Filed September 23, 2014	:	Examiner **Not Yet Assigned**
AQUEOUS LIQUID PREPARATION CONTAINING 2-AMINO-3-(4-BROMOBENZOYL)PHENYLACETIC ACID	:	**Mail Stop: AMENDMENT**

RESPONSE

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir/Madam:

In response to the Examiner's request, we are enclosing herewith six Terminal Disclaimers to overcome the double patenting rejection over the claims for the above-identified application.

Respectfully submitted,

/Warren M. Cheek, Jr./

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November 5, 2014

The USPTO is hereby authorized to charge any fees under 37 C.F.R. §§ 1.16, 1.17, and 1.492, which may be required by this paper to Deposit Account No. 23-0975.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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Shirou SAWA	:	**Confirmation No. 7395**
Serial No. 14/493,903	:	Group Art Unit **Not Yet Assigned**
Filed September 23, 2014	:	Examiner **Not Yet Assigned**
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TERMINAL DISCLAIMER UNDER 37 CFR 1.321

Commissioner for Patents
P.O. Box 1450
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Sir/Madam:

The owner, SENJU PHARMACEUTICAL CO., LTD., of 100% interest in the instant application, hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application, which would extend beyond the expiration date of the full statutory term defined in 35 USC 154 and 173, as shortened by any terminal disclaimer, of prior Patent No. 8,129,431, issued March 6, 2012. The owner hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and the prior patent are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors or assigns.

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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

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[] The undersigned is an attorney of record.

/Warren M. Cheek, Jr./

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Date: 2014.11.05 13:03:38 -05'00'

November 5, 2014

Warren M. Cheek
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Terminal disclaimer fee under 37 CFR 1.20(d) is included.

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Named Inventor	:	Attorney Docket No. 2014-1250
Shirou SAWA	:	**Confirmation No. 7395**
Serial No. 14/493,903	:	Group Art Unit **Not Yet Assigned**
Filed September 23, 2014	:	Examiner **Not Yet Assigned**
AQUEOUS LIQUID PREPARATION CONTAINING 2-AMINO-3-(4-BROMOBENZOYL)PHENYLACETIC ACID	:	**Mail Stop: AMENDMENT**

TERMINAL DISCLAIMER UNDER 37 CFR 1.321

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir/Madam:

The owner, SENJU PHARMACEUTICAL CO., LTD., of 100% interest in the instant application, hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application, which would extend beyond the expiration date of the full statutory term defined in 35 USC 154 and 173 as shortened by any terminal disclaimer filed prior to the grant of any patent granted on pending second Application Number 14/269,692, filed May 5, 2014. The owner hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and any patent granted on the second application are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon grantee, its successors or assigns.

In making the above disclaimer, the owner does not disclaim the terminal part of any patent granted on the instant application that would extend to the expiration date of the full statutory term as defined in 35 USC 154 and 173 of any patent granted on the second application, as shortened by any terminal disclaimer filed prior to the patent grant, in the event that any such granted patent: expires for failure to pay a maintenance fee; is held unenforceable; is found invalid by a court of competent jurisdiction; is statutorily disclaimed in whole or terminally

disclaimed under 37 CFR 1.321; has all claims cancelled by a reexamination certificate; is reissued; or is in any manner terminated prior to the expiration of its full statutory term as shortened by any terminal disclaimer filed prior to its grant.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

[X] The undersigned is empowered to act on behalf of the organization.

[] The undersigned is an attorney of record.

November 5, 2014

/Warren M. Cheek, Jr./

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Date: 2014.11.05 13:04:28 -05'00'

Warren M. Cheek
Reg. No. 33,367

Terminal disclaimer fee under 37 CFR 1.20(d) is included.

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Electronic Patent Application Fee Transmittal

Application Number:	14493903
Filing Date:	23-Sep-2014
Title of Invention:	AQUEOUS LIQUID PREPARATION CONTAINING 2-AMINO-3-(4-BROMOBENZOYL)PHENYLACETIC ACID
First Named Inventor/Applicant Name:	Shirou SAWA
Filer:	Warren M. Cheek Jr./Donna King
Attorney Docket Number:	2014-1250

Filed as Large Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
Statutory or Terminal Disclaimer	1814	6	160	960
		Total in USD ($)		**960**

Electronic Acknowledgement Receipt

EFS ID:	20613730
Application Number:	14493903
International Application Number:	
Confirmation Number:	7395
Title of Invention:	AQUEOUS LIQUID PREPARATION CONTAINING 2-AMINO-3-(4-BROMOBENZOYL)PHENYLACETIC ACID
First Named Inventor/Applicant Name:	Shirou SAWA
Customer Number:	513
Filer:	Warren M. Cheek Jr./maurice linder
Filer Authorized By:	Warren M. Cheek Jr.
Attorney Docket Number:	2014-1250
Receipt Date:	05-NOV-2014
Filing Date:	23-SEP-2014
Time Stamp:	15:20:46
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Credit Card
Payment was successfully received in RAM	$960
RAM confirmation Number	1619
Deposit Account	230975
Authorized User	CHEEK JR., WARREN M.

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

Charge any Additional Fees required under 37 C.F.R. Section 1.16 (National application filing, search, and examination fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.17 (Patent application and reexamination processing fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.19 (Document supply fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.20 (Post Issuance fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.21 (Miscellaneous fees and charges)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Supplemental Response or Supplemental Amendment	AttachA.pdf	173152 a516df9fd1395b60c15c9b3a41ba1193e9eab5cc	no	1
Warnings:					
The PDF file has been signed with a digital signature and the legal effect of the document will be based on the contents of the file not the digital signature.					
Information:					
2	Terminal Disclaimer Filed	AttachB.pdf	180109 2427f748c76b5bb1fd58d57f4e1aed00196c6391	no	2
Warnings:					
The PDF file has been signed with a digital signature and the legal effect of the document will be based on the contents of the file not the digital signature.					
Information:					
3	Terminal Disclaimer Filed	AttachC.pdf	180147 d453db652b6cb4ec4c5d7c06aa052cbc12bc7866	no	2
Warnings:					
The PDF file has been signed with a digital signature and the legal effect of the document will be based on the contents of the file not the digital signature.					
Information:					
4	Terminal Disclaimer Filed	AttachD.pdf	180126 05fd548e549367278418d18963f541789d01af0a	no	2
Warnings:					
The PDF file has been signed with a digital signature and the legal effect of the document will be based on the contents of the file not the digital signature.					
Information:					
5	Terminal Disclaimer Filed	AttachE.pdf	180121 962157932fa039e651ef21f6be29945a08496f99	no	2
Warnings:					
The PDF file has been signed with a digital signature and the legal effect of the document will be based on the contents of the file not the digital signature.					
Information:					
6	Terminal Disclaimer Filed	AttachF.pdf	180272 38f01d5e92ff115cc59c23e7902b628f81f8b0fd	no	2
Warnings:					

The PDF file has been signed with a digital signature and the legal effect of the document will be based on the contents of the file not the digital signature.

Information:

7	Terminal Disclaimer Filed	AttachG.pdf	180225 4287bb56a5569308bca6e83cd6c75104a0f15e51	no	2

Warnings:

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Information:

8	Fee Worksheet (SB06)	fee-info.pdf	30986 526f5fa19e03cf6073155a62d6e6eced75892fa5	no	2

Warnings:

Information:

Total Files Size (in bytes):	1285138

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Named Inventor	:	Attorney Docket No. 2014-1250
Shirou SAWA	:	**Confirmation No. 7395**
Serial No. 14/493,903	:	Group Art Unit **Not Yet Assigned**
Filed September 23, 2014	:	Examiner **Not Yet Assigned**
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Commissioner for Patents
P.O. Box 1450
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Sir/Madam:

The owner, SENJU PHARMACEUTICAL CO., LTD., of 100% interest in the instant application, hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application, which would extend beyond the expiration date of the full statutory term defined in 35 USC 154 and 173, as shortened by any terminal disclaimer, of prior Patent No. 8,497,304, issued July 30, 2013. The owner hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and the prior patent are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors or assigns.

In making the above disclaimer, the owner does not disclaim the terminal part of any patent granted on the instant application that would extend to the expiration date of the full statutory term as defined in 35 USC 154 and 173 of the prior patent, as presently shortened by any terminal disclaimer, in the event that it later: expires for failure to pay a maintenance fee; is held unenforceable; is found invalid by a court of competent jurisdiction; is statutorily disclaimed in whole or terminally disclaimed under 37 CFR 1.321; has all claims cancelled by a

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/Warren M. Cheek, Jr./

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Date: 2014.11.05 13:03:22 -05'00'

November 5, 2014

Warren M. Cheek
Reg. No. 33,367

Terminal disclaimer fee under 37 CFR 1.20(d) is included.

WMC/dlk
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Alexandria, VA 22313-1450

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Date: 2014.11.05 13:03:06 -05'00'

November 5, 2014

Warren M. Cheek
Reg. No. 33,367

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Named Inventor	:	Attorney Docket No. 2014-1250
Shirou SAWA	:	**Confirmation No. 7395**
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Alexandria, VA 22313-1450

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In making the above disclaimer, the owner does not disclaim the terminal part of any patent granted on the instant application that would extend to the expiration date of the full statutory term as defined in 35 USC 154 and 173 of the prior patent, as presently shortened by any terminal disclaimer, in the event that it later: expires for failure to pay a maintenance fee; is held unenforceable; is found invalid by a court of competent jurisdiction; is statutorily disclaimed in whole or terminally disclaimed under 37 CFR 1.321; has all claims cancelled by a

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Reg. No. 33,367

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Named Inventor	:	Attorney Docket No. 2014-1250
Shirou SAWA	:	**Confirmation No. 7395**
Serial No. 14/493,903	:	Group Art Unit **Not Yet Assigned**
Filed September 23, 2014	:	Examiner **Not Yet Assigned**
AQUEOUS LIQUID PREPARATION CONTAINING 2-AMINO-3-(4-BROMOBENZOYL)PHENYLACETIC ACID	:	**Mail Stop: AMENDMENT**

INFORMATION DISCLOSURE STATEMENT

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir/Madam:

Pursuant to the provisions of 37 CFR 1.56, 1.97 and 1.98, Applicant requests consideration of the information listed on attached Form PTO/SB/08.

1a. [X] This Information Disclosure Statement is submitted:

within three months of the filing date (or of entry into the National Stage) of the above-entitled application, **or**

before the mailing of a first Office Action on the merits or the mailing of a first Office Action after the filing of an RCE,

and thus no certification and/or fee is required.

1b. [] This Information Disclosure Statement is submitted

after the events of above paragraph 1a and prior to the mailing date of a final Office Action or a Notice of Allowance or an action which otherwise closes prosecution in the application, and thus:

(1) [] the certification of paragraph 2 below is provided, or

(2) [] the fee of $180.00 ($90.00 for small entity) specified in 37 CFR 1.17(p) is enclosed.

1c. [] This Information Disclosure Statement is submitted:

after the mailing date of a final Office Action or Notice of Allowance or action which otherwise closes prosecution in the application, and prior to payment of the issue fee, and thus:

the certification of paragraph 2 below is provided, and

the fee of $180.00 ($90.00 for small entity) specified in 37 CFR 1.17(p) is enclosed.

2. It is hereby certified

a. [] that each item of information contained in this Information Disclosure Statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the Statement (37 C.F.R. § 1.97(e)(1)), or

b. [] that no item of information contained in the Information Disclosure Statement was cited in a communication from a foreign patent office in a counterpart foreign application and, to the knowledge of the person signing the certification after making reasonable inquiry, was known to any individual designated in §1.56(c) more than three months prior to the filing of the Statement (37 C.F.R. § 1.97(e)(2)).

3. For each non-English language reference listed on the attached Form PTO/SB/08, reference is made to one or more of the following:

a. [] a full or partial English language translation submitted herewith,

b. [] an International Search Report submitted herewith,

c. [] a foreign patent office search report or office action (in the English language) submitted herewith,

d. [] the concise explanation contained in the specification of the present application at page,

e. [] the concise explanation set forth in the attached English language abstract,

f. [] the concise explanation set forth below or on a separate sheet attached to the reference:

4. [] A foreign patent office search report citing one or more of the references is enclosed.

5. [] Statement Under 37 CFR 1.704(d) Each item of information contained in the information disclosure statement: (i) Was first cited in any communication from a patent office in a counterpart foreign or international application or from the office, and this communication was not received by any individual designated in § 1.56(c) more than thirty days prior to the filing of the information disclosure statement; or (ii) Is a communication that was issued by a patent office in a counterpart foreign or international application or by the Office, and this communication was not received by any individual designated in § 1.56(c) more than thirty days prior to the filing of the information disclosure statement.

Respectfully submitted,

/Warren M. Cheek, Jr./

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Date: 2014.10.16 11:38:06 -04'00'

Warren M. Cheek
Registration No. 33,367
Attorney for Applicant

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Telephone (202) 721-8200
Facsimile (202) 721-8250
October 16, 2014

Sheet 1 of 3

INFORMATION DISCLOSURE STATEMENT

FORM PTO/SB/08 A&B (*modified*)

U.S. DEPARTMENT OF COMMERCE
PATENT AND TRADEMARK OFFICE

LIST OF REFERENCES CITED BY APPLICANT(S)
(*Use several sheets if necessary*)

Date Submitted to PTO: October 16, 2014

ATTY DOCKET NO. 2014-1250	**SERIAL NO.** 14/493,903
FIRST NAMED INVENTOR Shirou SAWA	
FILING DATE September 23, 2014	**GROUP**

U.S. PATENT DOCUMENTS

*EXAMINER INITIAL		DOCUMENT NUMBER	DATE	NAME	CLASS	SUBCLASS	FILING DATE IF APPROPRIATE
	AA	8,129,431	3/2012	Sawa et al.			
	AB	6,107,343	8/2000	Sallmann et al.			
	AC	4,910,225	3/1990	Ogawa et al.			
	AD	5,603,929	2/1997	Desai et al.			
	AE	5,475,034	12/1995	Yanni et al.			
	AF	5,558,876	9/1996	Desai et al.			
	AG	6,274,609	8/2001	Yasueda et al.			
	AH	5,540,930	7/1996	Guy et al.			
	AI	2,880,130	3/1959	Johnson			
	AJ	2,880,138	3/1959	Johnson			
	AK	6,071,904	6/2000	Ali et al.			
	AL	5,597,560	1/1997	Bergamini et al.			

FOREIGN PATENT DOCUMENTS

		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION/ADDITIONAL INFORMATION YES	NO
	BA	2 013 188	9/1990	CA				
	BB	22042/88	3/1989	AU				
	BC	94/15597	7/1994	WO				
	BD	2 383 971	3/2001	CA				
	BE	02/13804	2/2002	WO				
	BF	0 274 870	7/1988	EP				
	BG	94/05298	3/1994	WO				

OTHER DOCUMENT(S) *(Including Author, Title, Date, Pertinent Pages, Etc.)*

	CA	Y. Hara, "Evaluation of New Drugs by Clinicians", Clinics & Drug Therapy, Vol. 19, No. 10, October 2000, pp. 1-2.
	CB	G. Smolin, M.D., "New Drugs in Ophthalmology", International Ophthalmology Clinics, Vol. 36, No. 2, 1996, pp. 1-9.

EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609; draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

INFORMATION DISCLOSURE STATEMENT

FORM PTO/SB/08 A&B (*modified*)

U.S. DEPARTMENT OF COMMERCE
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ATTY DOCKET NO.	SERIAL NO.
2014-1250	14/493,903
FIRST NAMED INVENTOR Shirou SAWA	
FILING DATE September 23, 2014	**GROUP**

	CC	ISTA News Release, XIBROM™, Bromfenac Ophthalmic Solution, 2007, p.1.
	CD	S. Prince et al., "Analysis of Benzalkonium Chloride and its Homologs: HPLC Versus HPCE[1]", Journal of Pharmaceutical and Biomedical Analysis, Vol. 19, pp. 877-882, 1999.
	CE	M. Doughty, "Therapeutics: Medicines Update *p18* Side-Effects of Anti-Epilepsy Drugs", Optician, Vol. 223, No. 5853, May 31, 2002, pp. 16-22.
	CF	I. Reddy, Ph.D., "Ocular Therapeutics and Drug Delivery", Technomics Publishing Co., Basel, pp. 42-43, 390, 1996.
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Examiner Initial if reference considered, whether or not citation is in conformance with MPEP 609; draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

INFORMATION DISCLOSURE STATEMENT

FORM PTO/SB/08 A&B (*modified*) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE LIST OF REFERENCES CITED BY APPLICANT(S) (*Use several sheets if necessary*) Date Submitted to PTO: October 16, 2014	**ATTY DOCKET NO.** 2014-1250	**SERIAL NO.** 14/493,903
	FIRST NAMED INVENTOR Shirou SAWA	
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	CU	FDA Website search of Orange Book (Patent and Exclusivity Search Results): Approved Drug Products with Therapeutic Equivalence Evaluations; Search Results for N203168, 2014.
	CV	FDA website search of Orange Book (Detail Record Search): Approved Drug Products with Therapeutic Equivalence Evaluations, Search Results for N203168, 2014.
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(54) SYSTEME POUR CONSERVER LES PREPARATIONS OPHTALMIQUES
(54) PRESERVATIVE SYSTEM FOR OPHTHALMIC FORMULATIONS

(57)

Stable, clear, antimicrobially effective, ophthalmic formulations are disclosed which provide an antimicrobially effective preservative. The formulations include an ophthalmologically effective amount of a drug, which is a -COON group-containing non-steroidal anti-inflammatory drug (NSAID) in combination with an antibiotic drug, and a preservative system formed of a quaternary ammonium preservative and a nonionic polyoxyethylated octylphenol surfactant, all in an aqueous vehicle. The preservative system can be used with other formulations which require the preservative to be ophthamologically acceptable and antimicrobially effective. These formulations are useful for treating diseases and/or conditions 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 ophthalmologically acceptable antibiotic is preferably tobramycin which has been found not to interfere with the rate of diffusion of the NSAID. The combination of the NSAID and antibiotic is particularly effective in simultaneously preventing and/or eliminating infection while preventing and/or eliminating inflammation.

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(54) **SYSTEME POUR CONSERVER LES PREPARATIONS OPHTALMIQUES**

(54) **PRESERVATIVE SYSTEM FOR OPHTHALMIC FORMULATIONS**

(57) Stable, clear, antimicrobially effective, ophthalmic formulations are disclosed which provide an antimicrobially effective preservative. The formulations include an ophthalmologically effective amount of a drug, which is a -COOH group-containing non-steroidal anti-inflammatory drug (NSAID) in combination with an antibiotic drug, and a preservative system formed of a quaternary ammonium preservative and a nonionic polyoxyethylated octylphenol surfactant, all in an aqueous vehicle. The preservative system can be used with other formulations which require the preservative to be ophthalmologically acceptable and antimicrobially effective. These formulations are useful for treating diseases and/or conditions 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 ophthalmologically acceptable antibiotic is preferably tobramycin which has been found not to interfere with the rate of diffusion of the NSAID. The combination of the NSAID and antibiotic is particularly effective in simultaneously preventing and/or eliminating infection while preventing and/or eliminating inflammation.

ABSTRACT OF THE DISCLOSURE

Stable, clear, antimicrobially effective, ophthalmic formulations are disclosed which provide an antimicrobially effective preservative. The formulations include an ophthalmologically effective amount of a drug, which is a -COOH group-containing non-steroidal anti-inflammatory drug (NSAID) in combination with an antibiotic drug, and a preservative system formed of a quaternary ammonium preservative and a nonionic polyoxyethylated octylphenol surfactant, all in an aqueous vehicle. The preservative system can be used with other formulations which require the preservative to be ophthamologically acceptable and antimicrobially effective. These formulations are useful for treating diseases and/or conditions 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 ophthalmologically acceptable antibiotic is preferably tobramycin which has been found not to interfere with the rate of diffusion of the NSAID. The combination of the NSAID and antibiotic is particularly effective in simultaneously preventing and/or eliminating infection while preventing and/or eliminating inflammation.

PRESERVATIVE SYSTEM FOR OPHTHALMIC FORMULATIONS

FIELD OF THE INVENTION

The present invention relates to improved ophthalmic formulations which use an improved preservative system comprising a quaternary ammonium preservative and a stabilizing amount of a nonionic polyoxyethylated octylphenol surfactant for ophthalmic formulations of carboxyl ("-COOH") group-containing non-steroidal anti-inflammatory drugs ("NSAIDs") and contain an opthalmologically acceptable antibiotic, preferably tobramycin. The invention also relates to methods of using these formulations for treating diseases and/or conditions 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. In addition, the formulation can be used to treat bacterial infection.

BACKGROUND OF THE INVENTION

To be ophthalmologically acceptable, a formulation must possess a number of characteristics to comply with

the general FDA requirements of being safe and effective. In that eyes are quite sensitive to pain, the formulation must be developed such that it causes little to no discomfort or stinging when administered. This feature is particularly important to insure user compliance and important in that such formulations are often administered in order to relieve pain or inflammation. The ophthalmic use of NSAID compounds was disclosed in U.S. Patent No. 4,454,151, where NSAID compounds (such as those described in U.S. Patents 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.

Due to the formation of this complex, the formulations did not 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.

An ophthalmic suspension containing a particular NSAID is disclosed in U.S. Patent No. 4,087,538 issued May 2, 1978. The suspension is aqueous based and can include benzalkonium chloride. Another ophthalmic formulation is disclosed in U.S. Patent No. 4,559,343 issued December 17, 1985. The formulation is aqueous based and includes an NSAID and a benzalkonium chloride preservative. A somewhat similar ophthalmic formulation is disclosed in U.S. Patent No. 4,607,038 issued August 19, 1986. This formulation includes a specific NSAID (pranoprofen) in an aqueous based formula with a known

preservative. U.S. Patent No. 4,474,751 issued October 2, 1984 discloses ophthalmic formulations which gel in the eye in order to increase the bioavailability of the drug. The '751 patent discloses a large number of different active ingredients and excipient material. When this disclosure is taken in view of the other patents discussed above and the publications cited in each of them, the vast number of different ways of creating an ophthalmic formulation becomes apparent. Although there may be a considerable number of possible formulations and variations thereof, only certain specific formulations will meet all the requirements for being ophthalmologically acceptable.

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. In order for an excipient to be ophthalmologically acceptable, it must be non-irritating to the eye in combination with other excipients and an active ingredient. The excipients must not prevent the active ingredient from penetrating the blood-aqueous barrier and/or diffusing through the various ocular substructures to the site where it is pharmacologically active. The excipients can interact with each other or the active drug. Accordingly, care in formulating is required in that so many materials may be used. These materials generally 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 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, diclofenac, 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.

European published application 306,984 (published March 15, 1989) discloses a stable, clear, antimicrobially effective, ophthalmic formulation containing an NSAID and a preservative system formed of a quarternary ammonium preservative and a nonionic surfactant all in an aqueous vehicle. Although the formulations of this European laid-open application are useful in treating diseases that are either caused by, associated with, or accompanied by inflammatory processes, there is no indication that the formulations of the European laid-open application are effective inpreventing or eliminating infection.

A need has continued to exist for a stable, clear, antimicrobial preservative effective ophthalmic formulation for NSAIDs with antibiotics using BAC as the preservative, and an improved preservative system for -COOH group containing ophthalmic drugs to overcome both inflammation and infection.

SUMMARY OF THE INVENTION

A primary object of the invention is to describe and disclose a formulation containing an ophthalmologically effective amount of an NSAID in combination with an antibiotic, a quaternary ammonium preservative and a stabilizing amount of a nonionic polyoxyethylated octylphenol surfactant, all in an aqueous vehicle.

A feature of the present invention is that it allows for the preparation of stable, i.e., clear and antimicrobially and antibiotically effective, NSAID-containing ophthalmic formulations without the need for an organo-mercurial preservative.

Another feature is that methods for treating ophthalmic diseases in mammals using the ophthalmic pharmaceutical formulations of the invention are provided.

An advantage of the present invention is that it is useful in the treatment of diseases or conditions 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 and eliminating infection.

These and other objects, advantages and features of the present invention will become apparent to those persons skilled in the art upon reading the details of the composition, manufacture and usage as more fully set forth below. Reference being made to the accompanying

general structural formulae forming a part hereof wherein like symbols refer to like molecular moieties throughout.

DETAILED DESCRIPTION AND PREFERRED EMBODIMENTS

Before the present compositions and processes for making and using such are disclosed and described, it is to be understood that this invention is not limited to the particular compositions, components or methods of use described as such compositions, components and methods may, of course, vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to be limiting since the scope of the present invention will be limited only by the appended claims.

It must be noted that as used in this specification and the appended claims, the singular forms "a", "an" and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "a pharmaceutically acceptable salt" includes mixtures of salts, references to "an NSAID" includes reference to mixtures of such NSAIDS, reference to "the method of administration" includes one or more different methods of administration known to those skilled in the art.

Definitions

As used herein, the term "NSAID" means an ophthalmologically acceptable carboxyl group containing non-steroidal anti-inflammatory drug. The NSAID's include, for example, flurbiprofen, ketorolac, diclofenac, indomethacin, suprofen, and the isomers, esters and pharmaceutically acceptable salts thereof.

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 and/or condition in a mammal, including:

(i) preventing the disease and/or condition, that is, causing the clinical symptoms of the disease not to develop;

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

(iii) relieving the disease and/or condition, 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" refers to the stability of the formulation prior to administration and means ability to withstand the U.S. Pharmacopia antimicrobial challenge put by a panel of microbes.

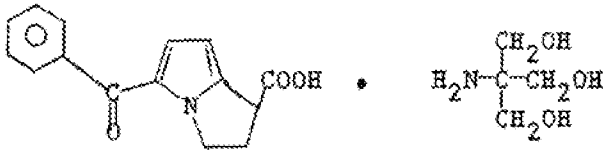
As used herein, the term "surfactant" means a nonionic surfactant, preferably ethoxylated octylphenol compounds as described below.

As used herein, the term "quarternary ammonium preservative" means a quarternary ammonium compound as described below.

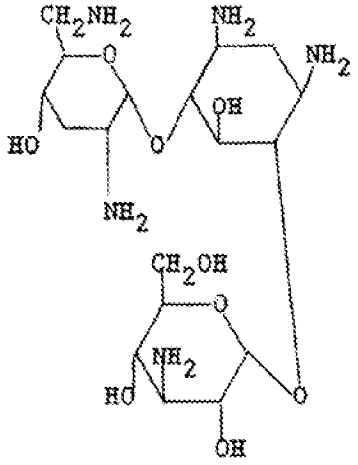
As used herein, the term "stabilizing" means keeping a formulation clear and antimicrobially effective for its minimum reasonable shelf life, e.g., at least one year.

"Ketorolac tromethamine" shall mean the compound (±)-5-benzoyl-1,2-dihydro-3H-pyrrolo-[1,2-a]-pyrrole-1-carboxylic acid 2-amino-2-hydroxymethyl-1,3-propanediol

salt, also known as (±)-5-benzoyl-2,3-dihydro-1H-pyrrolizine-1-carboxylic acid with 2-amino-2-(hydroxymethyl)-1,3-propanediol (1:1) having the following structural formula (I)



"Tobramycin" shall mean the antibiotic produced by streptomyces tinebrarius also known as O-3-amino-3-deoxy-a-D-glucopyranosyl-(1$6)-O-[2,6-diamino-2,3,6-trideoxy-a-D-ribo-hexopyranosyl-(1$4)]-2-deoxy-D-streptamine. Tobramycin is represented by the following structural formula II:



Tobramycin is a water soluble aminoglycosidic antibiotic having a broad spectrum of action against both gram negative and gram positive bacteria. Such

aminoglycosidic antibiotics are useful in treating ocular infections and are used prophylactically before and after ocular surgery.

Formulations

The formulations of the present invention include an NSAID active agent in an effective amount for ophthalmic treatment, an ophthalmologically acceptable antibiotic as a second active agent in an effective amount for ophthalmic treatment, a quaternary ammonium preservative, a stabilizing amount of a nonionic polyoxyethylated octylphenol surfactant, optionally including other excipients such as a chelating agent, a tonicifier, a buffering system, a viscosity agent as well as other stabilizing agents.

The NSAID is preferably flurbiprofen, ketorolac, diclofenac, indomethacin, suprofen, and the isomers, esters, and pharmaceutically acceptable salts thereof. The antibiotic is preferably tobramycin.

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., preferably 0.002% to 5% 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 to 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%.

*The active agent is the NSAID in combination with the antiobiotic.

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.;
Antibiotic	0.30% 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/ boric acid/ Na borate	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 carboxyl group-containing NSAIDs.

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

In addition to the NSAID there is another active ingredient in the form of an ophthalmologically acceptable antibiotic, preferably tobramycin. The antibiotic is present in an effective amount for ophthalmic treatment. The antibiotic tobramycin does not interfere with the corneal permeability of the NSAID.

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 octylphenol 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). Octoxynol 40 is a nonionic polymeric surfactant material. More specifically, it is a nonionic polyoxyethylated octylphenol surfactant material sold commercially by GAF.

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 to 8, preferably 6.8 to 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.

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. The inclusion of an antibiotic in the formulation does not effect the rate of diffusion of the NSAID.

Preferred Formulations

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 antibiotic is one which does not interfere with the corneal permeability of the NSAID. Tobramycin is a preferred antiobiotic.

The preferred ophthalmic solutions of the invention include a NSAID, benzalkonium chloride, Octoxynol 40 and disodium edetate and, as a second active agent, tobramycin.

A preferred ophthalmic NSAID/antibiotic solution has the following formulation:

Ingredient	Amount
NSAID	0.50% wt/vol.
antibiotic	0.30% 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/boric acid/ Na borate)	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 formulations is wherein the NSAID is Ketorolac Tromethamine and when the antibiotic is present it is tobramycin.

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 ophthalmic diseases, it supresses already developed inflammatory processes.

The formulation of the invention includes an antibiotic such as tobramycin, providing antibacterial properties useful in eliminating and/or preventing a bacterial infection.

Ophthalmic 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 to 10 drops of solution of active ingredient per day wherein the solution includes 0.5 wt/vol.% of Ketorolac trimethamine and 0.3 wt/vol.% of tobramycin.

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(s), preservatives and the excipients have not changed after a fixed period of time.

Preservative efficacy of the formulation prior to administration is tested by the procedure described in the U.S. Pharmacopia Compendiary, whereby a solution is challenged with a panel of microbes and a determination is made as to whether a given 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 and the antibiotic tobramycin.

Ingredient	Amount
ketorolac tromethamine	0.50% wt/vol.
tobramycin	0.30% 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	0.18% wt/vol.
Boric Acid	0.9% wt/vol.
Na Borate	0.45% 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 general pharmaceutical formulation for ophthalmic

administration containing an NSAID and an antibiotic.

Ingredient	Amount
NSAID	0.50% wt/vol.
antibiotic	0.3% 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	0.18% wt/vol.
Boric Acid	0.9% wt/vol.
Na Borate	0.45% wt/vol.

EXAMPLE 3

This example illustrates the preparation of a representative pharmaceutical formulation for ophthalmic administration containing the NSAID ketorolac tromethamine and tobramycin.

Ingredient	Amount
ketorolac tromethamine	0.50% wt/vol.
tobramycin	0.30% wt/vol
BAC (50% aq. soln.)	0.01% wt/vol.
Octoxynol 40 (70% aq. soln.)	0.01% wt/vol.
EDTA Na_2	0.20% wt/vol.
NaCl	0.18% wt/vol.
Boric Acid	0.9% wt/vol.
Na Borate	0.45% wt/vol.

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

formulation of any of these examples.

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	0.18% wt/vol.
Boric Acid	0.9% wt/vol.
Na Borate	0.45% 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.

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.

Formulations of the present invention are freely flowable liquids which can be administered directly to the eye using a conventional means such as eyedroppers. The amount of active ingredient administered will vary with the individual and/or the type of disease or condition being treated. The NSAID's such as ketorolac and antibiotics such as tobramycin are generally administered in an amount of about 1 to 2 drops per eye with drops containing about 25 microliters of formulation. The drops are generally administered 3 to 4 times per day.

EXAMPLE 6

In vitro rabbit corneal penetration of ketorolac was evaluated in the presence of tobramycin to determine if tobramycin alters penetration of ketorolac through rabbit corneas. Two sets of studies were performed to evaluate tobramycin's effect on ketorolac penetration.

Apparatus - A modified Franz diffusion cell consisting of an 8.0 ml glass receptor cell along with a teflon donor cell were used for the penetration experiments. A side arm allowed sampling of the receptor

phase. The donor cell was recessed to accommodate corneal curvature. A 0.3 ml volume of donor solution was placed on the epithelial side of the cornea, and evaporation of this donor solution was diminished by sealing a glass coverslip over the opening of the donor cell with silicon grease. To ensure corneal curvature throughout the course of the experiment, a 1.0 ml latex bulb was placed over the sampling port of the glass diffusion cell. By so doing, enough pressure was exerted under the cornea to maintain a curved, wrinkle-free membrane. Water at 37° C was circulated through the water jacket surrounding the receptor cell. A magnetic stir bar placed in the bottom of the receptor cell maintained homogeneity within the receptor solution.

Cornea Preparation - New Zealand white rabbits weighing 3.5 to 4 kg were used for the studies. Rabbits were sacrificed by rapid injection of 1.25 ml/kg of T-61 Euthanasia Solution (American Hoechst Corp. Animal Health Division, Somerville, NJ) into a marginal ear vein. The cornea were carefully removed along with 2-4 mm of surrounding scleral tissue then placed in a buffer containing: 0.57% sodium chloride, 0.361% sodium bicarbonate, 0.04% potassium chloride, 0.023% potassium phosphate dibasic, 0.007% magnesium sulfate, 0.08% calcium chloride, and 0.133% adenosine in water, adjusted to pH 7.4. This buffer was used as receptor solution for all studies; its selection was based on the ability to maintain corneal integrity throughout the diffusion studies.

Experimental Procedure - A fresh cornea was placed between the top and bottom of the teflon donor cell; this unit was then clamped onto the glass receptor cell. The receptor cell was filled with sterile, degassed buffer solution; all air bubbles were expelled from beneath the cornea by inverting the entire diffusion cell and

allowing bubbles to travel out the sampling port. After donor solution was placed on the cornea, a 0.3 ml sample of receptor solution was collected at the following time points: 15, 30, 45, 60 and 120 minutes. The 0.3 ml aliquot was replaced at each time point with fresh buffer solution.

Preparation of Test Solutions - 1. To determine ketorolac corneal diffusion in the presence of tobramycin, and to determine a dose effect, a saline vehicle was utilized to avoid potential complications by excipients. The following solutions were isotonic and prepared at pH 7.4: (a) 0.5% ketorolac tromethamine, 0.79% sodium chloride, purified water; (b) solution (a) with 0.15% tobramycin; (c) solution (a) with 0.30% tobramycin; and (d) solution (a) with 0.60% tobramycin.

2. To evaluate whether 0.30% tobramycin (a clinically acceptable and efficacious concentration) has an effect on ketorolac corneal diffusion when administered in a more complex vehicle, an isotonic solution at pH 7.4 was made which contained the following: (a) 0.5% ketorolac tromethamine, 0.79% sodium chloride, edetate disodium, benzalkonium chloride, purified water; (b) solution (a) with 0.30% tobramycin.

^{14}C-glycerol Penetration - To monitor corneal integrity throughout the course of the permeability studies, ^{14}C-glycerol penetration was evaluated (^{14}C-glycerol 15.76 mCi/mmole was obtained from NEN with a radiochemical purity of 98%). Nonionized ^{14}C-glycerol was incorporated into selected test solutions (1a and d, above). For controls, two additional isotonic test solutions were made at pH 7.4: (1) phosphate buffered saline; (2) 0.6% tobramycin in phosphate buffered saline. To a 2.0 ml aliquot of each test solution, 10 µl of ^{14}C-glycerol was added. At designated time intervals, 0.3 ml of receptor solution

was sampled for scintillation counting (Beckman model LS 8100).

Analytical Methods - 1. Quantitation of ketorolac was performed by HPLC. The mobile phase was composed of methanol, water and glacial acetic acid (65:34:1). The equipment included: a Spectra-Physics 8440 UV/Vis detector; a Spectra-Physics 4270 integrator; a Spectra-Physics 8700 solvent delivery system; a Dynatech autosampler; and a Whatman Partisil ODS 3, 10 micron column. The mobile phase flow rate was 1.0 ml/min; the sample injection volume was 50 µl; and the absorbance wavelength was 254 nm. A 100 µl aliquot of each sample was diluted with 150 µl of mobile phase.

2. Quantitation of tobramycin was performed using the Syva EMIT tobramycin assay kit. The assay is an enzyme immunoassay intended to quantitatively analyze tobramycin in human serum or plasma; the limit of detection is 1.0 µg/ml. The assay is based on competition for antibody sites between free drug in sample and drug labeled with glucose-6-phosphate dehydrogenase (G-6-P-DH). Since G-6-P-DH activity decreases upon binding with antibody, tobramycin concentration can be measured in terms of enzyme activity. Active enzyme converts oxidized nicotinamide adenine dinucleotide (NAD) to NADH. This conversion results in an absorbance change that is measured spectrophotometrically.

Each experiment was performed with matched controls; that is, from a single rabbit, one cornea was treated with a ketorolac (control) solution, and the other cornea was treated with the ketorolac and tobramycin solution. Each test solution containing tobramycin was evaluated in triplicate. For the study using the simple isotonic vehicle, data for nine control corneas were generated. Since these were control cornea, each is from a different

rabbit; hence, the deviation shown at each time point gives an indication of both the biological as well as experimental deviation inherent to this type of study.

An indication of corneal integrity throughout the course of these studies was determined by penetration of ^{14}C-glycerol. Changes in the permeability profile of ^{14}C-glycerol can be attributed to corneal alteration or damage. Select vehicles were chosen to evaluate whether corneal damage could be attributed to a particular compound or combination. With phosphate buffered saline serving as control, a two or three-fold increase in ^{14}C-glycerol penetration would indicate substantial corneal alteration. Table I shows that ^{14}C-glycerol penetration in a solution containing ketorolac tromethamine, or 0.6% tobramycin, or their combination, does not differ from its penetration in buffer alone. These results suggest that corneal integrity is not altered by ketorolac tromethamine or tobramycin.

TABLE I

Preparation	Percent of Initial Counts per Minute at 60 min	at 120 min
Phosphate Buffered Saline	2.10	7.36
Ketorolac tromethamine in Saline	2.47	8.60
Tobramycin (0.6%) in Phosphate buffered saline	1.83	7.08
Ketorolac tromethamine and Tobramycin (0.6%) in Saline	2.01	6.03

The average total milligrams of ketorolac penetrating the cornea at each time point for the simple solutions containing ketorolac alone and solutions

containing either 0.15%, 0.30% or 0.60% tobramycin, respectively, were compared. In all cases, the solutions containing tobramycin were equivalent to the control solution.

A comparison of the average total milligrams of ketorolac penetrating the cornea at each time point for the ophthalmic formulation with and without 0.30% tobramycin was made. Again, the test solution and the control solution were equivalent. Studies with the formulation demonstrated that after 60 minutes, there occurs a two to three fold increas in ketorolac diffusion, that is, enhanced penetration.

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;

an ophtalmologically acceptable antibiotic in an effective amount for ophthalmic treatment;

a quaternary ammonium preservative;

a stabilizing amount of a nonionic polyoxyethylated octylphenol surfactant; and

an aqueous vehicle.

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

3. The ophtalmologically acceptable non-steroidal anti-inflammatory drug formulation of Claim 1 wherein said nonionic polyoxyethylated octylphenol surfactant is Octoxynol 40 and the antibiotic is tobramycin.

4. The ophthalmologically acceptable non-steroidal anti-inflammatory drug formulation of Claim 1 including disodium edetate.

5. The ophthalmologically acceptable non-steroidal anti-inflammatory drug formulation of Claim 1 wherein said ophthalmologically acceptable non-steroidal anti-inflammatory carboxyl group-containing drug is selected from the group: ketorolac, indomethacin, flurbiprofen, diclofenac, and suprofen.

6. The ophthalmologically acceptable non-steroidal anti-inflammatory drug formulation of Claim 5 wherein said ophthalmologically acceptable non-steroidal anti-inflammatory carboxyl group-containing drug is ketorolac tromethamine.

7. The ophthalmologically acceptable non-steroidal anti-inflammatory drug formulation of Claim 1 comprising:

NSAID	0.001% to 10.0% wt/vol.;
Antibiotic	0.001% to 10.0% wt/vol.;
Preservative	0.001% to 1.0% wt/vol.;
Surfactant	0.001% to 1.0% wt/vol.; and
Purified Water	q.s. to 100%.

8. The ophthalmologically acceptable non-steroidal anti-inflammatory drug formulation of Claim 7 comprising:

ketorolac tromethamine	0.001% to 10.0% wt/vol.;
tobramycin	0.001% to 10.0% wt/vol.;
Preservative	0.001% to 1.0% wt/vol.;
Surfactant	0.001% to 1.0% wt/vol.; and
Purified Water	q.s. to 100%.

9. The ophthalmologically acceptable non-steroidal anti-inflammatory drug formulation of Claim 7 wherein said preservative is benzalkonium chloride, and the surfactant is Octoxynol 40.

10. The ophtalmologically acceptable non-steroidal anti-inflammatory drug formulation of

Claim 8, further comprising:

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 7.4%0.4.

11. The ophtalmologically acceptable non-steroidal anti-inflammatory drug formulation of Claim 9 comprising:

ketorolac tromethamine	0.50% wt/vol.;
Tobramycin	0.30% 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	0.18% wt/vol.;
Boric Acid	0.9% wt/vol.
Na Borate	0.45% wt/vol.
1N NaOH or 1N HCl	q.s. to adjust pH to 7.4%0.4; and
Purified Water	q.s. to 100%.

12. The use of a formulation comprising: an ophthalmologically acceptable non-steroidal anti-inflammatory carboxyl group-containing drug in an effective amount for ophthalmic treatment, an antibiotic in an effective amount for ophthalmic treatment, a quaternary ammonium preservative, a stabilizing amount of a nonionic polyoxyethylated octylphenol surfactant, and an aqueous

vehicle for treating ophthalmic disease in a mammal suffering therewith.

13. The use of Claim 12 wherein said preservative is benzalkonium chloride and said surfactant is Octoxynol 40.

14. The use of Claim 12 wherein said ophthalmologically acceptable non-steroidal anti-inflammatory carboxyl group-containing drug is selected from the group: ketorolac, indomethacin, flurbiprofen, diclofenac, and suprofen.

15. The use of Claim 12 wherein said ophthalmologically acceptable non-steroidal anti-inflammatory carboxyl group-containing drug is Ketorolac Tromethamine and the antibiotic is tobramycin.

16. The use of Claim 15 wherein said ophthalmologically acceptable non-steroidal anti-inflammatory drug formulation comprises:

ketorolac tromethamine	0.50% wt/vol.;
Tobramycin	0.30% wt/vol.;
BAC (50% aq. soln.)	0.01% wt/vol.;
Octoxynol 40 (70% aq. soln.)	0.01% wt/vol.;
EDTA Na_2	0.10% wt/vol.;
NaCl	0.18% wt/vol.;
Boric Acid	0.9% wt/vol.
Na Borate	0.45% wt/vol.
1N NaOH or 1N HCl	to adjust pH to 7.4%0.4; and
Purified Water	q.s. to 100%.

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(57) Claim

1. An ophthalmic NSAID formulation comprising: a NSAID in an effective amount for ophthalmic treatment, a quaternary ammonium preservative, a stabilizing amount of a nonionic ethoxylated octylphenol surfactant, and an aqueous vehicle.

22. An antimicrobially effective ophthalmologically acceptable preservative system for ophthalmologically acceptable, carboxyl group-containing drugs, said preservative system comprising a quaternary ammonium preservative and a stabilizing amount of a nonionic ethoxylated octylphenol surfactant.

Form 10

COMMONWEALTH OF AUSTRALIA

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Complete Spesification for the invention entitled:

PRESERVATIVE SYSTEM FOR OPHTHALMIC FORMULATIONS

The following statement is a full description of this invention, including the best method of performing it known to : US

PRESERVATIVE SYSTEM FOR OPHTHALMIC FORMULATIONS

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. Patent No. 4,454,151, where NSAID compounds (such as those described in U.S. Patents 4,089,969; 4,232,038; 4,087,539 and 4,097,579) were exemplified in formulation with $NaH_2PO_4 \cdot H_2O$, $Na_2HPO_4 \cdot H_2O$, NaCl, benzalkonium chloride ("BAC") and sterilized water. While the formulations described

in the '151 patent were efficacious, an insoluble complex was found to form between the NSAID and the BAC. The formulations became cloudy or turbid and did not, therefore, have the stability desired for shelf life in commercial applications. A reasonable minimum shelf life (that is, the time during which a solution remains clear and retains its pharmaceutical activity) is at least about one year, representing sufficient time to package, ship, and store a formulation without having to replace expired stock too frequently. The solutions of the present invention have shown a shelf life of at least one year. 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 diffuses 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.), forming insoluble complexes which cause the solution to become cloudy or turbid. Such a complex between the anionic drug and benzalkonium chloride can cause a decrease in the pharmaceutical activity of the anionic drug.

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

In the past, as in the case with other ophthalmic drugs that contain a -COOH group, antiinflammatory solutions of NSAIDs for occular use have proven to be incompatible with quaternary ammonium compounds such as BAC. This incompatibility is due to the fact that the -COOH group can form a complex with the quaternary ammonium compounds, rendering the preservative less available to serve its function, and reducing the activity of the active ingredient. Indomethacin ophthalmic formulations have been prepared, however, these are suspensions, not solutions. Ocufen Ophthalmic solution, an NSAID (flurbiprofen) approved by the FDA for ophthalmic use, incorporates thimerosal (with EDTA) as its preservative system. In U.S. patent 4,454,151 there is a disclosure of an ophthalmic formulation using ketorolac, benzalkonium chloride (as the preservative) and polysorbate 80, however the solution became cloudy or turbid after a short period of time.

It has remained desired to provide a stable, clear, antimicrobially effective ophthalmic formulation with a prolonged shelf life for -COOH group containing ophthalmic drugs, especially NSAIDs, using BAC as the preservative.

SUMMARY OF THE INVENTION

It has now been discovered that stable, clear and antimicrobially effective, NSAID-containing ophthalmic formulations can be prepared which include a quaternary ammonium preservative. These solutions have an improved shelf life, exhibiting no cloudiness or turbidity over extended periods.

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 an ethoxylated octylphenol as a nonionic surfactant, all in an aqueous vehicle.

Another aspect is an ophthalmic composition including an ophthalmologically effective amount of a NSAID, a quaternary ammonium preservate and a stabilizing amount of an ethoxylated octylphenol as a nonionic surfactant.

Another aspect is an ophthalmic composition including an ophthalmologically effective amount of a NSAID, benzalkonium chloride as a preservative and a stabilizing amount of an ethoxylated octylphenol as a nonionic surfactant.

Another aspect is an ophthalmic composition including an ophthalmologically effective amount of a NSAID, benzalkonium chloride as a preservative and a stabilizing amount of Octoxynol 40 as a nonionic surfactant.

Another aspect is an ophthalmic composition including an ophthalmologically effective amount of ketorolac or an isomer, an ester, or a pharmaceutically acceptable salt thereof, benzalkonium chloride as a preservative and a stabilizing amount of Octoxynol 40 as a nonionic surfactant.

In another 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. The NSAID's include, for example, flurbiprofen, ketorolac, diclofenac, indomethacin, and the isomers, esters, and pharmaceutically acceptable salts thereof.

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 "surfactant" means a nonionic surfactant, preferably ethoxylated octylphenol compounds as described below.

As used herein, the term "quaternary ammonium preservative" means a quaternary ammonium compound such as described below.

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 an NSAID active agent in an effective amount for ophthalmic treatment, a quaternary ammonium preservative, a stabilizing amount of an ethoxylated octylphenol as 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., preferably 0.002% to 5% wt/vol, most preferably 0.005% to 1% wt/vol 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 to 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	0.002% to 5.0% wt/vol.;
BAC (50% aq. soln.)	0.002% to 1.0% wt/vol.;
Octoxynol 40 (70% aq. soln.)	0.001% to 1.0% wt/vol.;
EDTA Na_2	0.01% to 1.0% 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%.

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

Ingredient	Amount
NSAID	0.005% to 1.0% wt/vol.;
BAC (50% aq. soln.)	0.002% to 1.0% wt/vol.;
Octoxynol 40 (70% aq. soln.)	0.001% to 1.0% wt/vol.;
EDTA Na_2	0.01% to 1.0% 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%.

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

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; and
Purified Water	q.s. to 100%.

The invention relates primarily to formulations having as the active agent ophthalmologically acceptable drugs [including the isomers (as either the (d)- or (l)-isomer) 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. Patent No. 4,454,151 to Waterbury, issued June 12, 1984, the pertinent portions of which are incorporated herein by reference), indomethacin, flurbiprofen sodium, and diclofenac, including the isomers, 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 benzalkonium chloride, preferably, benzalkonium chloride.

The nonionic surfactants useful in the formulations of the present invention are preferably ethoxylated octylphenol compounds, such as octylphenoxypoly-(ethyleneoxy)ethanols, more preferably, a homologous series of surfactants sold under the trade name Igepal CA with a numerical suffix indicating the mole ratio of ethylene oxide to octylphenol, the ratio being 3 to 40. Examples include Octoxynol 9, Octoxynol 12, Octoxynol 13, and Octoxynol 40, 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 to 8, preferably 6.8 to 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 as the preservative.

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

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

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

Ingredient	Amount
NSAID	0.002% to 5.0% wt/vol.;
BAC (50% aq. soln.)	0.002% to 1.0% wt/vol.;
Octoxynol 40 (70% aq. soln.)	0.001% to 1.0% wt/vol.;
EDTA Na_2	0.01% to 1.0% 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%.

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

Ingredient	Amount
NSAID	0.005% to 1.0% wt/vol.;
BAC (50% aq. soln.)	0.002% to 1.0% wt/vol.;
Octoxynol 40 (70% aq. soln.)	0.001% to 1.0% wt/vol.;
EDTA Na_2	0.01% to 1.0% 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%.

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 or an isomer thereof.

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 ophthalmic diseases, it supresses already developed inflammatory processes.

Ophthalmic 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, of 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 to 10 drops of 0.5% 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 or their isomers, salts or esters, 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.)	0.02% 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 or their isomers, salts or esters, 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 their isomers, salts or esters, 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, in the concentrations shown in the table below, 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.

Three surfactants were evaluated for their ability to dissolve the ketorolac - benzalkonium chloride complex and maintain a physically clear solution over an extended period of time. The three surfactants tested were: Octoxynol 40; Polysorbate 80 (Tween 80); and Myrj 52. Two concentrations of each surfactant were incorporated into the ophthalmic formulation, and these were placed at various temperatures for future visual observations.

	Octoxynol 40		Tween 80		Myrj 52	
	0.004%	0.02%	0.0035%	0.01%	0.0015%	0.01%
1 month						
60°C	clear	clear	clear	clear	clear	clear
40°C	clear	clear	very turbid	very turbid	turbid	turbid
RT	clear	clear	turbid	turbid	clear	clear
4-40°C	clear	clear	turbid	turbid	clear	clear
5 month						
60°C	clear	clear	clear	clear	clear	clear
40°C	clear	clear	turbid	turbid	turbid	turbid
RT	clear	clear	turbid	turbid	turbid	turbid

At the 5 month time period it was apparent that the Octoxynol 40 surfactant was superior to the other two surfactants. At 5 months, Tween 80 and Myrj 52 displayed turbidity when stored at RT. The presence of turbidity suggested the inability to solubilize a precipitate formation between the Ketorolac moiety and benzalkonium chloride.

A further study has shown a 2 year shelf life for the ophthalmic formulation. Precipitate formation and turbidity are not a problem with this formulation. Preservative efficacy is maintained throughout the 2 year shelf life.

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.

EXAMPLE 7

The objective of this clinical efficacy study was to compare the effectiveness and safety of ketorolac with a control solution in reducing inflammation following cataract removal and intraocular lens implantation. All patients underwent an extracapsular cataract extraction with intraocular lens implantation 1 day following initiation of treatment.

Ophthalmic examinations were performed preoperatively (within 3 weeks of surgery) and during the first week (postoperative days 1 to 3), second week (postoperative days 4 through 12), and third week (postoperative days 15 through 27) of treatment. Particular attention was given to signs and symptoms consistent with inflammation. Among the ocular characteristics assessed on a scale of none, mild, moderate, or severe were: lid edema, corneal edema, conjunctival injections, ciliary flush, and the presence of cells and flare in the anterior chamber.

Fluorophotometry: Anterior segment inflammation (i.e., iritis, cyclitis, iridocyclitis) is by definition a disruption of the blood-aqueous barrier. When inflammation is present, a careful slit lamp examination will reveal cells and flare within the anterior chamber of the eye. The clinical grading of cells and flare is a measure of degree of anterior segment inflammation; but consistent grading of these observations is difficult, even by experts.

Ocular fluorophotometry is based on the fact that the blood-aqueous barrier becomes permeable to

intravascular cells and proteinaceous fluid (explaining the observed cells and flare) and also to intravascular fluorescein. Furthermore, the appearance of fluorescein within the anterior chamber is a more sensitive indication of the breakdown of the blood-aqueous barrier than the gross observation of cells and flare, and is consistently quantifiable. For these reasons, a Flurortron® Master (Coherent, Sunnyvale, California), complete with software modifications designed for this study was used. Following oral administration of fluorescein, the fluorophotometer was used to determine the integrity of the aqueous barrier by measuring the concentration of fluorescein in the anterior chamber.

The fluorophotometry data were analyzed using the Wilcoxon Rank Sum Test or analysis of variance (ANOVA) of rank-transformed data by calculating the percentage difference in fluorescein concentration between the patient's two eyes, according to the formula:

Percent difference = [(fluorescein concentration of operated eye - fluorescein concentration of unoperated eye)/fluorescein concentration of unoperated eye] x 100.

This calculation allowed and corrected for any interpatient variation in the timing and concentration of fluorescein administered.

129 patients began treatment for 21 days with either ketorolac or vehicle. In this study, the ketorolac formulation used was that illustrated in Example 1 above. During the first week 118 patients and during the second week 110 patients were evaluated for postoperative inflammation with ophthalmic examinations and fluorophotometry. During the third week, 83 patients were evaluated with ophthalmic examinations alone. At 2 weeks ketorolac provide significantly greater anti-inflammatory activity than the vehicle as measured

by fluorophotometry (p = 0.019). When patients were excluded who had greater than 40% difference in fluorescein concentration between eyes at baseline, the p-value during week 2 rose to 0.06. In addition, the vehicle-treated patients had more ocular inflammation seen on slit lamp examination, e.g., eyelid edema (p = 0.001), conjunctival injection (p = 0.001), and Descemet folds (p = 0.002) than did the ketorolac-treated patients. Finally, there were significantly more complaints (p = 0.01) and more severe complaints consistent with ocular inflammation (photophobia, iritis, conjunctival injection) in the vehicle-treated group than in the ketorolac-treated group.

In summary, ketorolac solutions proved significantly superior to vehicle in treating postoperative inflammation as quantitated by fluorophotometry, by routine slit lamp examination, by patients having fewer and milder adverse events, and by infrequent need of additional corticosteroid therapy to control inflammation.

EXAMPLE 8

This was a double-blind, parallel comparison with vehicle to evaluate the efficacy of ketorolac 0.5% ophthalmic solution in reducing signs and symptoms of allergic conjunctivitis. Ketorolac 0.5% solution or a vehicle solution of the same pH and tonicity were instilled four times daily into the eyes of patients with allergic conjunctivitis (ocular itching with and without eosinophils seen on conjunctival scrapings) for 7 days.

Thirty patients with allergic conjunctivitis participated in the study. Following admission to the study, patients reported to the investigator for baseline, mid-week, and final one-week examinations. At each of these visits, patients received ophthalmic

examinations (visual acuity, external eye exam using slit lamp biomicroscopy, measurement of intraocular pressure, and undilated ophthalmoscopic examination). Laboratory tests included a conjunctival scraping performed at baseline and the final exam.

All patients completed the study. There were no adverse events or toxicities in patients treated with vehicle while stinging on one occasion was reported from ketorolac 0.5% ophthalmic solution. Ketorolac treatment was associated with a decrease in free eosinophilic granules as compared to vehicle ($p = 0.025$ Fisher's Exact Test. two-tailed).

The results of this study show that ketorolac 0.5% ophthalmic solution applied four times daily for seven days produces a decrease in eosinophilic granules as compared to vehicle in the treatment of allergic conjunctivitis.

EXAMPLE 9

This study was a double-blind, paired comparison design trial to evaluate the tolerance of ketorolac 0.5% ophthalmic solution and its vehicle in 26 healthy subjects. Solutions were instilled three times daily for 21 days. Complete ophthalmic examinations were done pretreatment and on days 3, 10, 17, 24 (2 days after ending treatment), and 45 (23 days after ending treatment). No statistically significant difference in symptoms (burning, stinging, itchiness, scratchiness, photophobia) or signs (tearing, ocular discharge, conjunctival vasodilation, chemosis, keratitis, fluorescein staining, Rose Bengal staining) was found between ketorolac and vehicle.

EXAMPLE 10

An ocular formulation containing 5 mg/ml ketorolac tromethamine was administered at a dose of 0.1 ml/eye every one-half hour for a total of 12 doses to both eyes of 6 New Zealand albino rabbits. The formulation contained benzalkonium chloride as the preservative system. Two additional groups of animals served as saline and vehicle controls, respectively.

Eyes were examined after the last dose was administered and on days 1, 2, 3, and 6 following dosing. Results indicated that no eye irritation or toxicity resulted from ketorolac tromethamine administration.

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:~~

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. An ophthalmic NSAID formulation comprising: a NSAID in an effective amount for ophthalmic treatment, a quaternary ammonium preservative, a stabilizing amount of a nonionic ethoxylated octylphenol surfactant, and an aqueous vehicle.

2. The ophthalmic NSAID formulation of Claim 1 wherein said quaternary ammonium preservative is benzalkonium chloride.

3. The ophthalmic NSAID formulation of Claim 1 wherein said nonionic ethoxylated octylphenol surfactant is an octylphenoxypoly(ethyleneoxy)ethanol with a mole ratio of ethylene oxide to octylphenol of between 3:1 and 40:1.

4. The ophthalmic NSAID formulation of Claim 3 wherein said nonionic ethoxylated octylphenol surfactant is Octoxynol 40.

5. The ophthalmic NSAID formulation of Claim 4 including disodium edetate.

6. The ophthalmic NSAID formulation of Claim 1 wherein said NSAID is selected from the group: ketorolac, indomethacin, flurbiprofen, and diclofenac, or their isomers, pharmaceutically acceptable salts, or esters.

7. The ophthalmic NSAID formulation of Claim 6 wherein said NSAID is Ketorolac Tromethamine.

8. The ophthalmic NSAID formulation of Claim 6 wherein said NSAID is the (l)-isomer of ketorolac or one of its pharmaceutically acceptable salts.

9. The ophthalmic NSAID formulation of Claim 1 comprising:

NSAID	0.001% to 10.0% wt/vol.;
Preservative	0.001% to 1.0% wt/vol.;
Surfactant	0.001% to 1.0% wt/vol.; and
Purified Water	q.s. to 100%.

10. The ophthalmic NSAID formulation of Claim 9 wherein said preservative is benzalkonium chloride.

11. The ophthalmic NSAID formulation of Claim 10 wherein said surfactant is Octoxynol 40.

12. The ophthalmic NSAID formulation of Claim 11 wherein said NSAID is Ketorolac Tromethamine.

13. The ophthalmic NSAID formulation of Claim 9 including:

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.

14. The ophthalmic NSAID formulation of Claim 13 comprising:

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	0.79% wt/vol.;
1N NaOH or 1N HCl	q.s. to adjust pH to 7.4 ±0.4; and
Purified Water	q.s. to 100%.

15. The ophthalmic NSAID formulation of Claim 14 wherein said NSAID is Ketorolac Tromethamine.

16. A method of treating ophthalmic disease comprising administering to a mammal suffering therewith a formulation comprising: a NSAID in an effective amount for ophthalmic treatment, a quaternary ammonium preservative, a stabilizing amount of a nonionic surfactant, and an aqueous vehicle.

17. The method of treating ophthalmic diseases of Claim 16 wherein said preservative is benzalkonium chloride.

18. The method of treating ophthalmic diseases of Claim 17 wherein said surfactant is Octoxynol 40.

19. The method of treating ophthalmic diseases of Claim 16 wherein said NSAID is selected from the group: ketorolac, indomethacin, flurbiprofen, and diclofenac, or their isomers, pharmaceutically acceptable salts, or esters.

20. The method of treating ophthalmic diseases of Claim 19 wherein said NSAID is Ketorolac Tromethamine.

21. The method of treating ophthalmic diseases of Claim 20 wherein said ophthalmic NSAID formulation comprises:

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.;
1N NaOH or 1N HCl	to adjust pH to 7.4 ± 0.4; and
Purified Water	q.s. to 100%.

22. An antimicrobially effective ophthalmologically acceptable preservative system for ophthalmologically acceptable, carboxyl group-containing drugs, said preservative system comprising a quaternary ammonium preservative and a stabilizing amount of a nonionic ethoxylated octylphenol surfactant.

23. The preservative system of Claim 22 wherein said ophthalmologically acceptable preservative is benzalkonium chloride and said surfactant is Octoxynol 40.

~~24. The use of a formulation of Claim 1 for the treatment or prevention of ocular inflammatory diseases.~~

24. The use of a preservative system of Claim 22 for the treatment or prevention of ocular inflammatory diseases.

25. A process for the preparation of an ophthalmic NSAID formulation which comprises mixing

0.001% to 10.0% wt/vol. of an NSAID,

0.001% to 1.0% wt/vol. of a preservative,

0.001% to 1.0% wt/vol. of a nonionic ethoxylated octylphenol surfactant, q.s. of 1N NaOH or 1N HCl to adjust pH to 6.0 to 8.0 and

Purified Water q.s. to 100%.

26. The process of Claim 25 which further comprises mixing

0.01% to 1.0% wt/vol. of a chelating agent,

q.s. of a tonicifier to achieve isotonicity with lacrimal fluid.

DATED this 14th day of August, 1991.

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(57) Abstract

An ophthalmic solution generally includes an ophthalmologically acceptable drug formulation incompatible with benzalkonium chloride and lauralkonium chloride present in an anti-microbially effective amount. The incompatibility of the ophthalmologically acceptable drug manifests itself by forming insoluble ion pairs with the benzalkonium chloride. It has been found that lauralkonium chloride which is the C_{12} homolog of benzalkonium chloride is effective as a preservative without apparent interaction with the acidic ophthalmologically acceptable drug and formulations maintain their antimicrobial efficiency over periods of up to one year or more.

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OPHTHALMIC COMPOSITIONS COMPRISING BENZYLLAURYLDIMETHYLAMMONIUM CHLORIDE

The present invention generally relates to improved ophthalmic formulations and solutions and more particularly to improved preservative systems for ophthalmologically acceptable drug formulations which have an incompatibility with benzalkonium chloride. More specifically, the present invention pertains to the preservative for an anti-inflammatory drug such as sodium flurbiprofen (Ocufen®).

Ophthalmologically acceptable drug formulations generally contain effective compounds and a number of ophthalmologically acceptable excipients. Such excipients generally include solutions, ointments, and suspensions, etc. More specifically, such excipients include stabilizing agents, surfactants, buffering systems, chelating systems, viscosity agents, and, importantly, a preservative.

Ophthalmic formulations, understandably, must be sterile and if a multi-dose regime is intended, the formulation must be preserved with an effective antimicrobial agent.

As discussed in U.S. Patent No. 5,110,493, organo-mercurials have been used extensively as the preservatives in ophthalmic solutions. As reported in this reference, these compounds pose difficulties due to potential mercury toxicity as well as poor chemical stability.

Therefore, benzalkonium chloride, which is a quaternary ammonium compound, has been widely used in ophthalmic solutions. It is also well-known, however, that benzalkonium chloride is considered incompatible with anionic drugs, forming insoluble compounds which cause the solution to turn cloudy.

This is because of the fact that many acidic drug entities carry a negative charge at physiological pH. In fact, all acidic drug entities will carry a negative charge at all pH above their pKa.

In the case of benzalkonium chloride, which is a positively charged preservative, ion pairs can be formed with negatively charged drug compounds, forming an insoluble ion pair which causes the drug to precipitate out of solution. Concomitant with the removal of the drug from solution is the removal of benzalkonium chloride, thereby rendering this quaternary germicide incapable of performing its function as an antimicrobial agent.

Benzalkonium chloride is a mixture of alkyldimethylbenzyl-ammonium chloride of the general formula as shown below in which R represents a mixture of the alkyls from C_8H_{17} to $C_{18}H_{37}$

As hereinbefore noted, it is well-known that benzalkonium chloride is generally incompatible with anionic detergents or anionic drug compounds.

See U.S. Patent No. 5,110,493, and The Merck Index, 11th Edition, Merck & Co., Inc., 1989.

The present invention specifically relates to the discovery that a particular member of a group of compounds, generally known as benzalkonium chloride, exhibits properties totally different from other members of the group and different from the gross properties of the mixture known as benzalkonium chloride.

This discovery by the applicant must be taken in the context that all compositions are made of the same substances, retaining their fixed chemical properties. The elements are capable of an infinity of permutations, and selection of that group or element of a group which proves serviceable to a given need requires a high degree of originality. This general premise relates to the invention at hand. The applicant has discovered that lauralkonium chloride, which is the C_{12} homolog of benzalkonium chloride, is compatible with acidic drug entities with apparently no insoluble ion pairs being formed therewith. This is contrary to the properties of the mixture of alkyldimethylbenzylammonium chloride, known as benzalkonium chloride, which includes a mixture of the alkyls from C_8H_{17} to $C_{18}H_{37}$.

SUMMARY OF THE INVENTION

An ophthalmic solution, in accordance with the present invention, generally includes an ophthalmologically acceptable drug formulation incompatible with benzalkonium chloride and lauralkonium chloride present in an antimicrobially effective amount. More specifically, flurbiprofen is an example of an acidic drug that forms an insoluble ion-

pair with benzalkonium chloride. However, when combined with lauralkonium chloride, no apparent insoluble ion pairs are formed.

More particularly, in accordance with the present invention, the ophthalmic solution may further include citric acid monohydrate, sodium citrate dihydrate, polyvinyl alcohol, edetate disodium dihydrate, sodium chloride, potassium chloride and water.

The amount of lauralkonium chloride is any antimicrobially effective amount and preferably may be up to about 0.005% by weight per volume of the solution, and the amount of sodium flurbiprofen may be present in any effective amount and preferably about 0.03% by weight per volume.

The combination of lauralkonium chloride is further emphasized in that it can be combined with an acidic ophthalmologically acceptable drug formulation having a negative charge at physiological pH, and further the fact that the acidic ophthalmologically acceptable drug is capable of forming an insoluble ion-pair with benzalkonium chloride, no apparent insoluable ion-pairs are produced when the drug is in combination with lauralkonium chloride, taken itself.

Further, the invention includes a method for preserving an acidic ophthalmologically acceptable drug solution, comprising adding to the ophthalmologically acceptable drug solution an antimicrobially effective amount of lauralkonium chloride.

DETAILED DESCRIPTION

Flurbiprofen is a classic example of an acidic drug that forms an insoluble ion-pair with benzalkonium chloride. It has been discovered that this interaction (insoluble ion-pair formation) can be overcome by formulating the flurbiprofen with the C_{12} homolog of benzalkonium chloride and lauralkonium chloride.

The lauralkonium chloride utilized will comprise at least 95% and preferably about 97.8% of the C_{12} homolog, 1.5% of the C_{14} homolog, and 0.7% of the C_{16} homolog.

The following examples, illustrating the utility of lauralkonium chloride as opposed to benzalkonium chloride, include the preparation or compounding of flurbiprofen formulations as follows.

Compounding occurs in two parts:

Part 1: Disperse polyvinyl alcohol in rapidly stirring purified water and heat to 85°C. Maintain temperature and stirring for one hour to dissolve the polyvinyl alcohol.

Part 2: While mixing a bulk of purified water of at least 50% of the final lot volume, add edetate disodium, benzalkonium chloride or lauralkonium chloride, potassium chloride, sodium chloride, sodium citrate and citric acid allowing each to dissolve or mix well before adding the next. Adjust the pH to 6.4-6.6 with dilute sodium hydroxide and/or hydrochloric acid. Add sodium flurbiprofen to the bulk and mix well.

While mixing Part 2, add Part 1 and mix thoroughly. Adjust the pH to 6.4-6.6 with dilute sodium hydroxide and/or hydrochloric acid. Sterilize the lot by filtration (0.22μ) and aseptically fill units into pre-sterilized containers.

The benzalkonium chloride and the lauralkonium chloride utilized in the present examples were obtained from E.M. Industries, Inc. of Hawthorne, NY and Triple Crown Ammerica, Inc. of Perkasie, PA, respectively.

Example

Table 1 shows the ingredients for Examples A and B, with the formulations being identical, except that Example A utilizes benzalkonium chloride and Example B utilizes lauralkonium chloride in the same amounts, i.e., 0.005%, by weight per volume.

TABLE 1

OCULEN® FORMULATIONS

Ingredient	Example A	Example B
	% w/v	% w/v
Sodium flurbiprofen	0.03	0.03
Benzalkonium chloride	0.005	-
Lauralkonium chloride	-	.005
Citric acid monohydrate USP	0.05	0.05
Sodium citrate dihydrate USP	0.45	0.45
Polyvinyl alcohol 20-90 Grade	1.4	1.4
Edetate disodium dihydrate USP	0.0127	0.0127

Sodium chloride USP	0.65	0.65
Potassium chloride USP	0.075	0.075
Purified water USP	qs to 100	qs to 100
Sodium hydroxide NF	pH 6.4 to 6.6	pH 6.4 to 6.6
Hydrochloric acid NF	pH 6.4 to 6.6	pH 6.4 to 6.6

Example A results in a cloudy solution with precipitate and loss of antimicrobial efficacy while Example B remains as a solution and the solution maintains its antimicrobial efficacy. Example A failed to pass the preservative effectiveness test as described in the British Pharmacopeia while Example B passes the British Pharmacopieia preservative effectiveness test.

In addition, the ability of lauralkonium chloride to stay in solution and to maintain its antimicrobial effectiveness as a function of time was also monitored. Table 2 shows the concentration of lauralkonium chloride in the formulation described in Example B. Table 3 shows the ability of lauralkonium chloride to maintain its antimicrobial efficacy over a period of up to one year or more.

TABLE 2

No. of Days	Lauralkonium chloride - ppm
13	46.0
32	46.0
75	45.8
115	45.0
192	47.7

370	48.2

TABLE 3

No. of Days	Microbiology Results
13	Pass BP-88
370	Pass BP-88

Although there has been hereinabove described a specific ophthalmic solution and method in accordance with the present invention, for the purpose of illustrating the manner in which the invention may be used to advantage, it should be appreciated that the invention is not limited thereto. Accordingly, any and all modifications, variations, or equivalent arrangements which may occur to those skilled in the art, should be considered to be within the scope of the present invention as defined in the appended claims.

WHAT IS CLAIMED IS:

1. An ophthalmic solution comprising:

an ophthalmologically acceptable drug formulation incompatible with benzalkonium chloride; and

a preservative consisting essentially of lauralkonium chloride and present in an antimicrobially effective amount.

2. The ophthalmic solution according to Claim 1 wherein said ophthalmologically acceptable drug formulation comprises sodium flurbiprofen.

3. The ophthalmic solution according to claim 2 further comprising citric acid monohydrate, sodium citrate dihydrate, polyvinyl alcohol, edetate disodium dihydrate, sodium chloride, potassium chloride, and water.

4. The ophthalmic solution according to Claims 1, 2 or 3 wherein said lauralkonium chloride is present in an amount up to about 0.005% by weight per volume of the solution.

5. The ophthalmic solution according to claim 2 or 3 wherein the sodium flurbiprofen is present in an amount up to about 0.03% by weight per volume of the solution and the lauralkonium chloride is present in an amount up to about 0.005% by volume of the solution.

6. An ophthalmic solution comprising:

an acidic ophthalmologically acceptable drug formulation having a negative charge at physiological pH; and

a preservative consisting essentially of lauralkonium chloride and present in an antimicrobially effective amount.

7. The ophthalmic solution according to Claim 6 wherein said ophthalmologically acceptable drug formulation comprises sodium flurbiprofen.

8. The ophthalmic solution according to Claim 7 further comprising citric acid monohydrate, sodium citrate dihydrate, polyvinyl alcohol, edetate disodium dihydrate, sodium chloride, potassium chloride, and water.

9. The ophthalmic solution according to Claims 6, 7 or 8 wherein said lauralkonium chloride is present in an amount up to about 0.005% by weight per volume of the solution.

10. The ophthalmic solution according to Claim 7 or 8 wherein the sodium flurbiprofen is present in an amount up to about 0.03% by weight per volume of the solution and the lauralkonium chloride is present in an amount up to about 0.005% by volume of the solution.

11. A method for preserving an acidic ophthalmically acceptable drug solution comprising adding to said ophthalmically acceptable drug solution an antimicrobially effective amount of lauralkonium chloride.

12. An ophthalmic solution comprising:

an acidic ophthalmologically acceptable drug capable of forming an insoluble ion-pair with benzalkonium chloride; and

a preservative consisting essentially of lauralkonium chloride and present in an antimicrobially effective amount.

INTERNATIONAL SEARCH REPORT

Inter. asl Application No
PCT/US 94/00188

A. CLASSIFICATION OF SUBJECT MATTER
IPC 5 A61K31/19 A61K9/00 A61K47/18

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 5 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CHEMICAL ABSTRACTS, vol. 112, no. 16, 16 April 1990, Columbus, Ohio, US; abstract no. 145590h, see abstract & JP,A,01 246 227 (SANTEN PHARMACEUTICAL CO.,LTD.) 2 October 1989	1,3,4,6, 8,9,11, 12
A	DATABASE WPI Week 8231, Derwent Publications Ltd., London, GB; AN 82-64749E (31) see abstract & JP,A,57 102 817 (KAKENYAKU KAKO KK) 26 June 1982	2,5,7,10

☐ Further documents are listed in the continuation of box C.

☐ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

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"P" document published prior to the international filing date but later than the priority date claimed

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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Date of the actual completion of the international search	Date of mailing of the international search report
11 April 1994	

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Scarponi, U

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter. nal Application No
PCT/US 94/00188

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
JP-A-01246227	21-05-75	JP-A- 50058310	21-05-75
		JP-B- 59016038	12-04-84
		US-A- 4091167	23-05-78
JP-A-57102817	26-06-82	NONE	

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(86) PCT/JP00/06014

(87) WO01/017527

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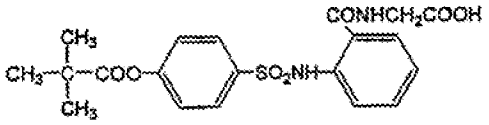
(54) MEDICAMENTS THERAPEUTIQUE ET PROPHYLACTIQUE POUR TRAITER LES MALADIES OPHTALMIQUES
(54) PROPHYLACTIC AND THERAPEUTIC MEDICAMENTS FOR OPHTHALMIC DISEASES

(57)
Preventive and therapeutic agents for eye diseases, particularly inflammatory eye diseases and corneal ulcer, containing as the active ingredient the compound of formula (I), pharmacologically acceptable salts thereof, or hydrates of both.



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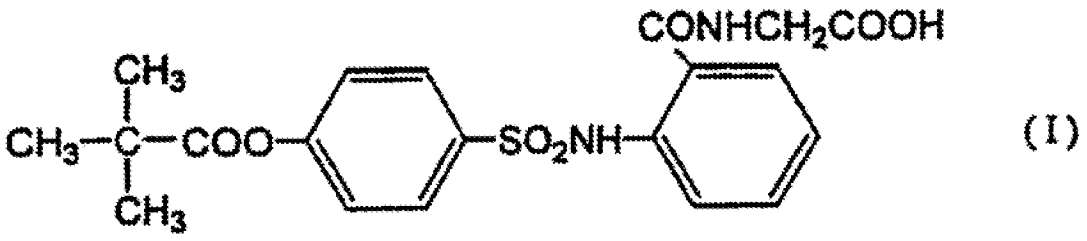
(54) Titre : MEDICAMENTS THERAPEUTIQUE ET PROPHYLACTIQUE POUR TRAITER LES MALADIES OPHTALMIQUES
(54) Title: PROPHYLACTIC AND THERAPEUTIC MEDICAMENTS FOR OPHTHALMIC DISEASES

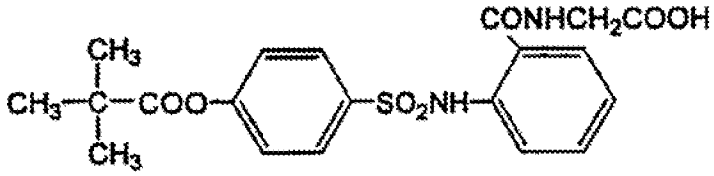


(I)

(57) Abrégé/Abstract:
Preventive and therapeutic agents for eye diseases, particularly inflammatory eye diseases and corneal ulcer, containing as the active ingredient the compound of formula (I), pharmacologically acceptable salts thereof, or hydrates of both.

Abstract of the disclosure:

The present invention provides a prophylactic and therapeutic medicament for ophthalmic diseases, especially ophthalmic inflammatory diseases and corneal ulcer, comprising as an active ingredient a compound represented by the formula (I):



(I)

or a pharmacologically acceptable salt or hydrate thereof.

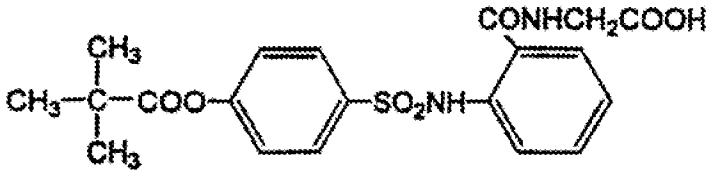
PROPHYLACTIC AND THERAPEUTIC MEDICAMENTS FOR OPHTHALMIC DISEASES

TECHNICAL FIELD

The present invention relates to a prophylactic and therapeutic medicament for ophthalmic diseases having a leukocyte (neutrophil)-derived elastase inhibitory activity.

BACKGROUND OF THE INVENTION

JP-B 5-81586 and JP-A 5-194366 (corresponding to EP-A 539223) disclose a compound represented by the formula (I):



(I)

(hereinafter referred to as a compound of Formula (I)) and a salt or hydrate thereof, which has a human neutrophil-derived elastase inhibitory activity and is effective for preventing and treating diseases such as pulmonary emphysema, atherosclerosis and rheumatoid arthritis.

On the other hand, the ophthalmologic field also

involves various diseases relating to leukocytes and their elastases. For example, ophthalmic infections, corneal traumas, corneal ulcers and uveitis may be mentioned. In an ophthalmic infection, the cellular infiltration of leukocytes results in an intraocular abscess [Invest. Ophthalmol. Vis. Sci., 40, 385-391 (1999)]. An alkaline trauma (erosion) which is one of corneal traumas allows leukocytes to be infiltrated into corneal stromal cells at an early stage of the alkaline erosion, two to three weeks after which the elevation of leukocyte elastase activity is observed [Ophthalmic. Res., 29, 154-160 (1997)]. Also in a case of corneal ulcers, a corneal wound or detachment results in the infiltration of leukocytes into a corneal stroma, which leads to the release or secretion of a protease such as an elastase or collagen [Klin. Monatsbl. Augenheilkd, 188, 593-595 (1986)]. An uveitis, especially Behcet's disease, was reported to undergo an increase in a plasma leukocyte elastase [Clin. Chim. Acta 236:129-134 (1995), Acta, Ophthalmol. Scand. 75:287-289 (1997), J.Reumatol. 25: 326-328 (1998)]. While leukocytes or their elastases were reported to be involved in the ophthalmic diseases mentioned above, no actual effect of the administration of an elastase inhibitor was reported.

While in JP-A 5-221872 (corresponding to EP-A 519354) and JP-A 6-509232 (corresponding to EP-A 596118), a microbe-derived substance having human leukocyte elastase inhibitory activity is described generally to be useful as a prophylactic and therapeutic medicament against a corneal scar tissue formation or a fibroblast proliferation [eye solidification (burn, mechanical or chemical damage, keratoconjunctivitis) and the like], it was not administered actually to verify its effect, and is different totally from a compound of Formula (I).

OBJECTS OF THE INVENTION

An objective of the present invention is to develop a prophylactic and therapeutic medicament for ophthalmic diseases containing as an active ingredient a compound of Formula (I).

This objective as well as other objectives and advantages of the present invention will be explained hereinafter with reference to the attached drawings.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 is a graph showing the effect of an eye drop formulation of N-[o-(p-pivaloyloxybenzenesulfonyl-amino)benzoyl]glycine monosodium salt tetrahydrate

(hereinafter referred to as Compound A) on an endotoxin-induced keratitis (effect on a corneal opacity). Each symbol represents a mean ± standard deviation (n=4). A statistically significant difference from a control is analyzed with $p<0.05$ (Wilcoxon test, one-sided).

Fig. 2 is a graph showing the effect of a Compound A eye drop formulation on an endotoxin-induced keratitis (effect on a corneal ulcer). Each symbol represents a mean ± standard deviation (n=4). A statistically significant difference from a control is analyzed with $p<0.05$ (Wilcoxon test, one-sided).

Fig. 3 is a graph showing the effect of a Compound A eye drop formulation on an endotoxin-induced keratitis (effect on a vascularization). Each symbol represents a mean ± standard deviation (n=4).

Fig. 4 shows the effect of a Compound A eye drop formulation 15 days after the challenge on an endotoxin-induced keratitis. Each column represents a mean ± standard deviation (n=4). A statistically significant difference from a control is analyzed with $p<0.05$ (Wilcoxon test, one-sided).

Fig. 5 is a graph showing the effect of a Compound A eye drop formulation on an alkaline erosion keratitis (effect on a corneal opacity). Each symbol represents

a mean ± standard deviation (n=4).

Fig. 6 is a graph showing the effect of a Compound A eye drop formulation on an alkaline erosion keratitis (effect on a corneal ulcer). Each symbol represents a mean ± standard deviation (n=4). A statistically significant difference from a control is analyzed with $p<0.05$ (Wilcoxon test, one-sided).

Fig. 7 is a graph showing the effect of a Compound A eye drop formulation on an alkaline erosion keratitis (effect on a vascularization). Each symbol represents a mean ± standard deviation (n=4).

Fig. 8 is a graph showing the effect of a Compound A eye drop formulation on a pyocyanic corneal ulcer immediately after the inoculation of the microbe. Each symbol represents a mean ± standard deviation (n=6). A statistically significant difference from a control is analyzed with $p<0.05$ (Wilcoxon test, one-sided).

Fig. 9 is a graph showing the effects of the instillation of Compound A and lomefloxacin on a pyocyanic corneal ulcer one day after the inoculation of the microbe and later. Each symbol represents a mean ± standard deviation (n=5-6). A statistically significant difference from a control is analyzed with * $p<0.05$ and ** $p<0.01$ (Steel test, one-sided).

SUMMARY OF THE INVENTION

The present inventors found out that a compound represented by Formula (I) or a pharmacologically acceptable salt or hydrate thereof exhibits a marked prophylactic and therapeutic effect against various ophthalmic diseases.

Thus, the present invention provides a prophylactic and therapeutic medicament for ophthalmic diseases, especially ophthalmic inflammatory diseases and corneal ulcer, comprising as an active ingredient a compound represented by Formula (I) or a pharmacologically acceptable salt or hydrate thereof.

The present invention also provides a method for preventing and treating an ophthalmic disease which comprises administering an active ingredient mentioned above to a mammal in need of a treatment for such ophthalmic disease.

Furthermore, the present invention provides use of an active ingredient mentioned above in the manufacture of a prophylactic and therapeutic medicament for ophthalmic diseases.

Moreover, the present invention provides an eye drop formulation in the form of an aqueous suspension of an active ingredient described above.

DETAILED DESCRIPTION OF THE INVENTION

The prophylactic and therapeutic medicament according to the present invention is preferably in a dosage form for a local administration such as an eye drop formulation or an ophthalmic ointment, which is useful for preventing and treating various ophthalmic diseases such as ophthalmic infections (for example, corneal herpes, bacterial keratitis, bacterial conjunctivitis, mycotic keratitis, acanthamebic keratitis, infectious endophthalmitis, infectious corneal ulcer and the like), corneal trauma, cicatricial keratoconjunctival diseases (for example, alkaline erosive keratoconjunctivitis, Stevens-Johnson syndrome, ophthalmic pemphigoid and the like), corneal ulcer (for example, Mooren's ulcer, corneal ulcer subsequent to chronic rheumatoid arthritis or collagen disease, Terrien's margine degeneration, catarrhal corneal ulcer, infectious corneal ulcer and the like), vitamin A insufficiency-induced keratomalacia, necrotic keratitis, neuroparalytic keratitis, diabetic keratophathy, keratoconjunctiva sicca, contact lens-induced keratoconjunctivitis, vernal conjunctivitis, allergic conjunctivitis, uveitis, Behcet's syndrome, inflammation after cataract surgery and pseudopterygium, especially a keratoconjunctival inflammatory disease

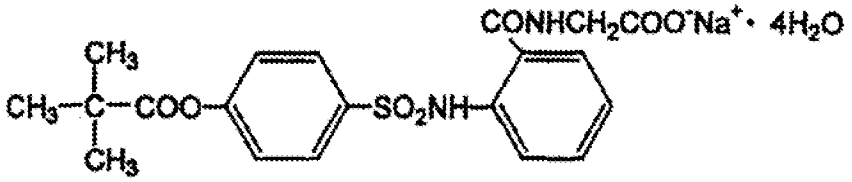
(for example, corneal herpes, bacterial keratitis, bacterial conjunctivitis, mycotic keratitis, acanthamebic keratitis, corneal trauma, alkaline erosive keratoconjunctivitis, corneal ulcer, vitamin A insufficiency-induced keratomalacia, necrotic keratitis, neuroparalytic keratitis, diabetic keratophathy, keratoconjunctiva sicca, contact lens-induced keratoconjunctivitis, vernal conjunctivitis, allergic conjunctivitis and the like). It is useful also for preventing and treating corneal ulcer (including various corneal ulcers described above and those induced otherwise), especially an infectious corneal ulcer.

A compound of Formula (I) used as an active ingredient according to the present invention or a pharmacologically acceptable salt thereof is a known compound described in JP-B 5-81586, and can be produced, in accordance with the procedure described therein, by the amidation of p-pivaloyloxybenzenesulfonyl chloride followed by the conversion into a salt by a known method. The resultant compound may also be converted into a hydrate by a known method.

A pharmacologically acceptable salt of a compound of Formula (I) may for example be an inorganic salt such as hydrochloride, hydrobromide, hydroiodide,

sulfate, phosphate and nitrate, an organic salt such as acetate, lactate, tartarate, benzoate, citrate, methanesulfonate, ethanesulfonate, benzenesulfonate, toluenesulfonate, isethionate, glucuronate and gluconate, an alkaline metal salt (sodium salt, potassium salt and the like), an alkaline earth metal salt (calcium salt, magnesium salt and the like), an ammonium salt, a pharmacologically acceptable amine salt (tetramethylammonium salt, triethylamine salt, methylamine salt, dimethylamine salt, cyclopentylamine salt, benzylamine salt, phenethylamine salt, piperidine salt, monoethanolamine salt, diethanolamine salt, tris(hydroxymethyl)aminomethane salt, lysine salt, arginine salt, N-methyl-D-glucamine salt and the like).

One preferred especially as an active ingredient used in the present invention is a sodium salt tetrahydrate of a compound of Formula (I), i.e., N-[o-(p-pivaloyloxybenzenesulfonylamino)benzoyl]glycine monosodium salt tetrahydrate (described in Example 3 in JP-A 5-194366 corresponding to EP-A 539223) represented by Formula (I-A):



(I-A)

The prophylactic and therapeutic medicament for ophthalmic diseases according to the present invention, on the basis of its leukocyte-derived elastase inhibitory activity, is useful in preventing and treating various ophthalmic diseases such as an ophthalmic infections (for example, corneal herpes, bacterial keratitis, bacterial conjunctivitis, mycotic keratitis, acanthamebic keratitis, infectious endophthalmitis, infectious corneal ulcer and the like), corneal trauma, cicatricial keratoconjunctival diseases (for example, alkaline erosive keratoconjunctivitis, Stevens-Johnson syndrome, ophthalmic pemphigoid and the like), corneal ulcer (for example, Mooren's ulcer, corneal ulcer subsequent to chronic rheumatoid arthritis or collagen disease, Terrien's margine degeneration, catarrhal corneal ulcer, infectious corneal ulcer and the like), vitamin A insufficiency-induced keratomalacia, necrotic keratitis, neuroparalytic keratitis, diabetic keratophathy, keratoconjunctiva sicca, contact lens-induced keratoconjunctivitis, vernal conjunctivitis, allergic conjunctivitis, uveitis, Behcet's syndrome, inflammation after cataract surgery and pseudopterygium, especially a keratoconjunctival inflammatory disease (for example, corneal herpes, bacterial keratitis,

bacterial conjunctivitis, mycotic keratitis, acanthamebic keratitis, corneal trauma, alkaline erosive keratoconjunctivitis, corneal ulcer, vitamin A insufficiency-induced keratomalacia, necrotic keratitis, neuroparalytic keratitis, diabetic keratophathy, keratoconjunctiva sicca, contact lens-induced keratoconjunctivitis, vernal conjunctivitis, allergic conjunctivitis and the like). It is useful also for preventing and treating corneal ulcer (including various corneal ulcers described above and those induced otherwise), especially infectious corneal ulcer.

The prophylactic and therapeutic medicament for ophthalmic diseases according to the present invention can be mixed with a pharmacologically acceptable carrier, excipient or diluent which is known per se and formulated by a method known per se into a pharmaceutical or a veterinary medicine in various oral or parenteral dosage forms such as tablets, capsules, granules, injection solutions, eye drops and ophthalmic ointments, and it is especially preferred to be used in a local dosage form, preferably an eye drop formulation or an ophthalmic ointment.

The eye drop formulation may for example be aqueous formulations such as aqueous eye drops, aqueous suspension eye drops, viscous eye drops and solubilized

eye drops as well as non-aqueous formulations such as non-aqueous eye drops and non-aqueous suspension eye drops, with an aqueous formulation being preferred. One preferred especially is an aqueous suspension eye drop formulation.

The aqueous eye drop formulation may contain various additives incorporated ordinarily, such as buffering agents (e.g., phosphate buffers, borate buffers, citrate buffers, tartarate buffers, acetate buffers, amino acids, sodium acetate, sodium citrate and the like), isotonicities (e.g., saccharides such as sorbitol, glucose and mannitol, polyhydric alcohols such as glycerin, concentrated glycerin, polyethylene glycol and propylene glycol, salts such as sodium chloride), preservatives or antiseptics (e.g., benzalkonium chloride, benzethonium chloride, p-oxybenzoates such as methyl p-oxybenzoate or ethyl p-oxybenzoate, benzyl alcohol, phenethyl alcohol, sorbic acid or its salt, thimerosal, chlorobutanol and the like), solubilizing aids or stabilizing agents (e.g., cyclodextrins and their derivative, water-soluble polymers such as polyvinyl pyrrolidone, surfactants such as polysorbate 80 (Tween 80)), pH modifiers (e.g., hydrochloric acid, acetic acid, phosphoric acid, sodium hydroxide, potassium hydroxide, ammonium hydroxide and

the like), thickening agents (e.g., hydroxyethyl cellulose, hydroxypropyl cellulose, methyl cellulose, hydroxypropylmethyl cellulose, carboxymethyl cellulose and their salts), chelating agents (e.g., sodium edetate, sodium citrate, condensed sodium phosphate) and the like.

The eye drop formulation in the form of an aqueous suspension may also contain suspending agents (e.g., polyvinyl pyrrolidone, glycerin monostearate) and dispersing agents (e.g., surfactants such as tyloxapol and polysorbate 80, ionic polymers such as sodium alginate) in addition to the additives listed above, whereby ensuring that the eye drop formulation is a further uniform microparticulate and satisfactorily dispersed aqueous suspension.

When the eye drop formulation in the form of an aqueous suspension is produced, it is preferable to use a pH modifier to make the formulation acidic pH (pH4 to 5.5). A preferred pH modifier is hydrochloric acid.

The eye drop formulation in the form of an aqueous suspension preferably contains sodium citrate or sodium acetate as a buffering agent, concentrated glycerin and/or propylene glycol as an isotonicity and polyvinyl pyrrolidone as a suspending agent. A preferred dispersing agent is a surfactant and/or sodium alginate.

Such surfactant is preferably tyloxapol or polysorbate 80.

The ophthalmic ointment may employ an ointment base known per se, such as purified lanolin, petrolatum, plastibase, liquid paraffin, polyethylene glycol and the like.

The prophylactic and therapeutic medicament of the present invention may be administered to a mammal which is or may be suffered from an ophthalmic disease (e.g., human, rabbit, dog, cat, cattle, horse, monkey). While the administration route and the dose may vary depending on a symptom, age and body weight of a subject, the concentration is about 0.001 to 5 (w/v) %, preferably about 0.01 to 3 (w/v) % as a free form of a compound of Formula (I) contained in an aqueous eye drop formulation when given to an adult, and is given preferably 1 to 8 times a day with a single dose being one to several drops.

When given as the ophthalmic ointment, the dose is about 0.001 to 5 (w/v) %, preferably about 0.01 to 3 (w/v) % as a free form of a compound of Formula (I), and is given preferably 1 to 4 times a day as appropriate in view of the symptom.

Unless the intended purpose of use is affected adversely, the prophylactic and therapeutic medicament

of the present invention may contain or may be used together with other appropriate pharmacologically effective substances, for example, steroidal anti-inflammatory agents (dexamethasone, prednisolone and the like), non-steroidal anti-inflammatory agents (diclofenac sodium, pranoprofen and the like), antiallergic agents (tranilast, ketotifen fumarate, sodium cromoglicate and the like), antihistamic agents (diphenhydramine hydrochloride and the like), glaucoma-treating agents (pilocarpine hydrochloride, physostigmine salicylate, timolol, isopropylunoprostone and the like), antibiotics (gentamycin sulfate, fradiomycin sulfate, tobramycin, sulbenicillin, cefmenoxime, erythromycin, colistin, oxytetracycline, polymyxin B, chloramphenicol, micronomicin, dibekacin, sisomicin and the like), antibacterial agents (sulfamethizole, sulfamethoxazole, ofloxacin, norfloxacin, lomefloxacin hydrochloride, enoxacin, ciprofloxacin hydrochloride, cinoxacin, sparfloxacin, tosufloxacin tosylate, nalidixic acid, pipemidic acid trihydrate, pipemidic acid, fleroxacin, levofloxacin and the like), and antiviral agents (idoxuridine, acyclovir and the like), and antimycotic agents (pimaricin, fluconazole, miconazole, amphotericin B, flucytosine, itraconazole and the like).

The prophylactic and therapeutic medicament of the present invention is used preferably together with at least one selected from the antibiotic, antibacterial, antiviral and antimycotic agents listed above in prophylaxis or therapy especially for an ophthalmic infection-induced inflammation or corneal ulcer. In such case, any of the antibiotic, antibacterial, antiviral and antimycotic agents can be combined with the prophylactic and therapeutic medicament of the present invention in a single formulation, or may be instilled separately. When being instilled separately, the prophylactic and therapeutic medicament of the present invention may be instilled simultaneously with any of the antibiotic, antibacterial, antiviral and antimycotic agents, or successively at a certain interval. When being instilled simultaneously, any of the prophylactic and therapeutic medicament of the present invention and the antibiotic, antibacterial, antiviral and antimycotic agents is first instilled and then preferably after a certain time period another agent is instilled whereby avoiding any escape of the agent given previously. Any of the antibiotic, antibacterial, antiviral and antimycotic agents listed above may also be given systemically by means of an oral or intravenous formulation.

The present invention is further illustrated in detail by the following Experiments and Examples, which are not construed to limit the scope of the present invention.

EXPERIMENT 1

The effect of Compound A on an ophthalmic inflammatory disease was investigated as described below.

The effect of Compound A when given as eye drops was investigated in a rabbit keratitis model using an endotoxin derived from Pseudomonas aeruginosa detected frequently in an ophthalmic infection as well as in a rabbit corneal alkaline erosion model.

MATERIALS AND METHODS

(1) Animals

Male Japanese albino rabbits each weighing about 2 to 2.5 kg purchased from FUKUZAKI rabbit-raising association were used. Each animal was maintained at a temperature of 24 ± 4°C and a humidity of 55 ± 15 %.

(2) Test substances

Compound A was given as a 1.0 % Compound A eye drop formulation prepared by suspending Compound A in a formulation base (0.1 % NaH_2PO_4, 0.1 % polysorbate 80 and 0.9 % NaCl, pH 5.0). As a positive control, a

0.1 % betamethasone eye drop formulation (Rinderon™ solution, Sionogi) was used. In a control group, the formulation base was given.

(3) Methods

1) Effect on endotoxin-induced keratitis

16 Male Japanese albino rabbits each weighing 2 to 2.5 kg were used. The rabbits were divided into four groups each having 4 animals, which were anesthetized systemically by an intramuscular administration each of 1 ml/kg of an equal volume mixture of 5 % ketamine hydrochloride and 2 % xylazine hydrochloride. Each 10 µl of a 1 % solution of Pseudomonas aeruginosa-derived endotoxin in physiological saline was infused into each corneal stroma of a rabbit. An anterior part of an eye was observed using a slit lamp every 5 days over a period from the day after the endotoxin infusion through the 30th day, and examined for the corneal opacity, the corneal ulcer and the vascularization, which were scored in accordance with the criteria shown in Table 1. Each test substance was started to be instilled immediately after the endotoxin infusion, and then given 4 times a day in the volume of 20 µl every 2 hours.

2) Effects on alkaline erosive keratitis

16 Male Japanese albino rabbits each weighing 2 to

2.5 kg were used. The rabbits were divided into four groups each having 4 animals, which were anesthetized systemically by an intramuscular administration each of 1 ml/kg of an equal volume mixture of 5 % ketamine hydrochloride and 2 % xylazine hydrochloride and also locally by an instillation of oxybuprocaine hydrochloride. A filter paper whose diameter was 10 mm and which had been immersed in 2N NaOH was brought into contact with the center of the right cornea of a rabbit for 1 minute to establish an alkaline erosion, and then the eye was rinsed immediately with 10 mL or more of physiological saline. The depth of the corneal ulcer and the vascularization were observed using a slit lamp every 5 days over a period from 5 days after the alkaline erosion through the 30th day, and scored in accordance with the criteria shown in Table 1. Each test substance was started to be instilled immediately after the alkaline erosion, and then given 4 times a day in the volume of 20 µl every 2 hours.

Table 1

Rabbit keratitis scoring criteria

* Corneal opacity[remarks 1)]

A) Degree

0: No opacity

1: Mild opacity but distinguishable anterior chamber

2: Difficulty in distinguishing details of iris

3: Almost no transparency in anterior chamber

B) Corresponding size of corneal region

1: 1/3 or less of entire

2: 1/3 to 2/3 of entire

3: 2/3 or more of entire

* Corneal ulcer

0: No corneal ulcer

1: Ulcer of less than 1/3 in depth from corneal surface toward inside of anterior chamber

2: Ulcer of 1/3 or more and less than 2/3 in depth from corneal surface toward inside of anterior chamber

3: Ulcer of 2/3 or more in depth from corneal surface toward inside of anterior chamber

4: Perforation in cornea

* Vascularization[remarks 1]

A) Length

0: No vascularization into cornea

1: Less than 1/3 from corneal limbus through center

2: Less than 2/3 from corneal limbus through center

3: 2/3 or more from corneal limbus through center

B) Region

0.5: Less than 1/3 of corneal circumference

1: 1/3 or more and less than 2/3 of corneal circumference

2: 2/3 or more of corneal circumference

Remarks 1) Each as score A x score B

RESULTS AND DISCUSSION

1) Effects on endotoxin-induced keratitis

Figs. 1 to 3 show the change in the keratitis symptoms over a period from 5 to 30 days after the endotoxin infusion. In the control group, the severity of each symptom peaked on the 15th day, and then a gradual recovery was observed until the 30th day when almost all disappeared. In Compound A instillation group, inhibitory effects were observed on all of the evaluation items, i.e., the corneal opacity, the corneal ulcer and the vascularization, when compared with the control group. In the 0.1 % betamethasone phosphate instillation group used as the positive control, the onset of the keratitis was inhibited almost completely over the observation period. Fig. 4 shows the total score in each group on the 15th day when the severity of each symptom peaked, and revealed that the % inhibition in the Compound A instillation group when compared with the control group was 59.4 %, with a statistically significant difference.

Based on the results described above, the Compound A eye drop formulation was proven to be effective

against various symptoms of the keratitis during an ophthalmic infection.

While betamethasone phosphate used here as a positive control exhibited an extremely potent anti-inflammatory activity, its use is limited frequently in view of a side effect experienced as the exacerbation of an infection over a prolonged therapy with a steroid in a clinical case of the ophthalmic infections.

Accordingly, the Compound A eye drop formulation expected to have a less risk of the exacerbation of an infection can serve as a hopeful agent against the ophthalmic infections.

2) Effects on alkaline erosive keratitis

Figs. 5 to 7 show the change in the keratitis symptoms over a period from 5 to 30 days after the corneal alkaline exposure. In the control group, the severity peaked on the 20 to 25th day after the corneal alkaline exposure. In Compound A instillation group, a significant inhibitory effect on the corneal ulcer was observed on the 20th day, but no effects were noted on the vascularization or the corneal opacity. In the 0.1 % betamethasone phosphate instillation group used as the positive control, a significant inhibitory effect was observed on the vascularization on the 15th day.

EXPERIMENT 2

MATERIALS AND METHODS

(1) Animals

Male Japanese albino rabbits each weighing about 2 kg purchased from KITAYAMA LABES CO., LTD. were used. Each animal was maintained at a temperature of 23 ± 3°C and a humidity of 55 ± 10 %.

(2) Test substances

Compound A was given as a 1.0 % Compound A eye drop formulation prepared by suspending Compound A in a formulation base (0.1 % sodium acetate, 0.1 % polysorbate 80 and 0.9 % NaCl, pH 5.0). A 0.3 % lomefloxacin (LFLX) hydrochloride was used as an antibacterial agent, and physiological saline was used as a control.

(3) Methods

1) Excision of nictitating membrane

After instilling 0.4 % oxybuprocaine hydrochloride for a local anesthesia, a nictitating membrane was excised.

2) Inoculation

A causative microorganism used was a clinical isolate Pseudomonas aeruginosa strain No. ho-134. A rabbit was anesthetized systemically with 5 % ketamine

hydrochloride and 2 % xylazine hydrochloride (equal volume mixture), and then inoculated by an infusion of 30 µl of a 3.9×10^4 CFU/ml cell suspension (1.17×10^3 CFU/cornea) using a 100 µl microsyringe fitted with a 30G needle into one corneal stroma of a rabbit.

3) Instillation

An animal which had received an infusion of the cell suspension into the corneal stroma and whose inoculation was surely successful was grouped into one of [1] physiological saline instillation group (control, n=6) and [2] 1.0 % Compound A instillation group (Compound A group, n=6) as groups whose therapy was started immediately after the inoculation, and [3] 1.0 % Compound A instillation group (late Compound A group, n=5), [4] 0.3 % LFLX instillation group (LFLX group, n=6) and [5] 1.0 % Compound A instillation - 0.3 % LFLX instillation combination group (Compound A - LFLX combination group, n=6) as groups whose therapy was started 1 day after the inoculation (after onset of corneal ulcer), and 50 µl of each substance was given four times a day immediately after the inoculation or 1 day after the inoculation (after onset of corneal ulcer). In the Compound A - LFLX combination group, the 1.0 % Compound A eye drop formulation was instilled about 10 minutes after the instillation of the 0.3 %

LFLX eye drop formulation.

4) Observation of infectious symptoms

Each animal was examined for the corneal ulcer every 24 hours after the inoculation and scored in accordance with the rabbit corneal lesion scoring criteria (Barletta J.P. et al., Invest Ophthalmol Vis Sic 37:20~28, 1996) shown in Table 2.

Table 2

Rabbit corneal lesion scoring criteria

* Corneal ulcer

0:No corneal ulcer

1:Ulcer of less than 1/4 of entire cornea

2:Ulcer of 1/4 or more and less than 1/2 of entire cornea

3:Ulcer of 1/2 or more and less than 3/4 of entire cornea

4:Ulcer of 3/4 or more of entire cornea

RESULTS AND DISCUSSION

1) Effects on pyocyanic corneal ulcer - effect of instillation started immediately after inoculation

The results of the instillation started immediately after the inoculation are shown in Fig. 8. The corneal ulcer was exacerbated gradually in the control group (physiological saline group) toward an

extensive corneal ulcer 5 days after the inoculation. On the contrary, the corneal ulcer formation was started to be inhibited 3 days after the inoculation in the Compound A group, with a statistically significant difference (Fig. 8).

2) Effects on pyocyanic corneal ulcer - effect of instillation started one day after inoculation

In the late Compound A group in which the instillation was started 1 day after the inoculation, the corneal ulcer formation was started to be inhibited 3 days after the inoculation. The LFLX group exhibited the change similar to that in the control group, with no inhibition of the corneal ulcer formation being noted (Fig. 9). In the Compound A - LFLX combination group, the corneal ulcer formation was started to be inhibited potently 3 days after the inoculation, with a statistically significant difference (Fig. 9).

Based on the results observed as described above, Compound A as an elastase inhibitor was proven to be effective against the corneal ulcer induced by bacterial infection. It was also proven that a combination of an elastase inhibitor with an antibacterial agent was more markedly effective against the corneal ulcer of a bacterial infection than each agent used alone.

EXAMPLE 1

An aqueous eye drop formulation was prepared using the following composition.

Component	Quantity
Compound A	0.1 g
Sodium chloride	0.9 g
Sodium acetate	0.1 g
Benzalkonium chloride	0.005 g
Hydrochloric acid	As appropriate
Sodium hydroxide	As appropriate
Sterilized purified water	to 100 mL (pH 6.0)

In about 80 ml of purified water, Compound A, sodium chloride, sodium acetate and benzalkonium chloride were dissolved. The solution was adjusted at pH 6.0 using hydrochloric acid and sodium hydroxide. Sterilized purified water was added to make the entire volume 100 mL, whereby obtaining an aqueous eye drop formulation.

EXAMPLE 2

An eye drop formulation as an aqueous suspension was prepared using the following composition.

Component	Quantity
Compound A	1.0 g

Sodium chloride	0.9 g
Sodium acetate	0.1 g
Polysorbate 80	0.2 g
Benzalkonium chloride	0.005 g
Hydrochloric acid	As appropriate
Sodium hydroxide	As appropriate
Sterilized purified water	to 100 mL (pH 5.0)

In about 80 ml of purified water, sodium chloride, sodium acetate, polysorbate 80 and benzalkonium chloride were dissolved. The solution was adjusted at pH 5.0 using hydrochloric acid and sodium hydroxide, and then Compound A was added and suspended uniformly using a homogenizer. Sterilized purified water was added to make the entire volume 100 mL, whereby obtaining an eye drop formulation as an aqueous suspension.

EXAMPLE 3

An eye drop formulation as an aqueous suspension was prepared using the following composition.

Component	Quantity
Compound A	0.5 g
Concentrated glycerin	2.6 g
Sodium acetate	0.1 g
Hydroxypropylmethyl cellulose	0.2 g

Methyl p-oxybenzoate	0.03 g
Propyl p-oxybenzoate	0.02 g
Hydrochloric acid	As appropriate
Sodium hydroxide	As appropriate
Sterilized purified water	to 100 mL (pH 5.0)

About 80 ml of purified water was warmed and methyl p-oxybenzoate and propyl p-oxybenzoate were dissolved. In this solution, hydroxypropylmethyl cellulose was dispersed and then cooled to room temperature for dissolution. To this solution, concentrated glycerin and sodium acetate were added, and then the pH was adjusted at 5.0 using hydrochloric acid and sodium hydroxide. To this solution, Compound A was added and suspended uniformly using a homogenizer. Sterilized purified water was added to make the entire volume 100 mL, whereby obtaining an eye drop formulation as an aqueous suspension.

Example 4

The following composition was used to make an ophthalmic ointment

Component	Quantity
Compound A	2.0 g
Liquid paraffin	2.0 g
White petrolatum	to 100 g

Liquid paraffin and white petrolatum were sterilized previously by heating. Subsequently, Compound A was mixed thoroughly with liquid paraffin, and then kneaded with the white petrolatum to obtain an ophthalmic ointment.

EXAMPLE 5

An eye drop formulation as an aqueous suspension was prepared using the following composition.

Component	Quantity
Compound A	1.0 g
Sodium citrate	0.1 g
Concentrated glycerin	1.2 g
Methyl p-oxybenzoate	0.026 g
Propyl p-oxybenzoate	0.014 g
Propylene glycol	1.0 g
Polyvinyl pyrrolidone (K-25)	0.5 g
Sodium alginate	0.2 g
Hydrochloric acid	As appropriate
Sterilized purified water	to 100 mL (pH 5.0)

In about 80 ml of purified water, sodium citrate, concentrated glycerin, methyl p-oxybenzoate, propyl p-oxybenzoate, propylene glycol and polyvinyl pyrrolidone were dissolved. In this solution, Compound A was dissolved and the solution was filtered through a 0.22

μm membrane filter, adjusted at pH 5.0 with hydrochloric acid, whereby precipitating a fine crystal (2 to 3 μm) of Compound A. Sodium alginate was dissolved, and purified water was added to make the entire volume 100 mL, whereby obtaining an eye drop formulation as an aqueous suspension.

After a storage for 4 weeks at 60°C, the eye drop formulation as an aqueous suspension contained 101.7 % of Compound A, and exhibited a satisfactory re-dispersion performance without any aggregation.

EXAMPLE 6

An eye drop formulation as an aqueous suspension was prepared using the following composition.

Component	Quantity
Compound A	1.0 g
Sodium citrate	0.1 g
Concentrated glycerin	1.2 g
Methyl p-oxybenzoate	0.026 g
Propyl p-oxybenzoate	0.014 g
Propylene glycol	1.0 g
Polyvinyl pyrrolidone (K-25)	0.5 g
Sodium alginate	0.2 g
Tyloxapol	0.1 g
Hydrochloric acid	As appropriate

Sterilized purified water	to 100 mL (pH 5.0)

In about 80 ml of purified water, sodium citrate, concentrated glycerin, methyl p-oxybenzoate, propyl p-oxybenzoate, propylene glycol and polyvinyl pyrrolidone were dissolved. In this solution, Compound A was dissolved and the solution was filtered through a 0.22 μm membrane filter, adjusted at pH 5.0 with hydrochloric acid, whereby precipitating a fine crystal (2 to 3 μm) of Compound A. Sodium alginate and tyloxapol were dissolved, and purified water was added to make the entire volume 100 mL, whereby obtaining an eye drop formulation as an aqueous suspension.

After a storage for 2 weeks at 60°C, the eye drop formulation as an aqueous suspension contained 102.5 % of Compound A, and exhibited a satisfactory re-dispersion performance without any aggregation.

EXAMPLE 7

An eye drop formulation as an aqueous suspension was prepared using the following composition.

Component	Quantity
Compound A	1.0 g
Sodium citrate	0.1 g
Concentrated glycerin	1.2 g
Methyl p-oxybenzoate	0.026 g

Propyl p-oxybenzoate	0.014 g
Polyvinyl pyrrolidone (K-25)	0.5 g
Sodium alginate	0.2 g
Tyloxapol	0.1 g
Hydrochloric acid	As appropriate
Sterilized purified water	to 100 mL (pH 5.0)

In about 80 ml of purified water, sodium citrate, concentrated glycerin, methyl p-oxybenzoate, propyl p-oxybenzoate and polyvinyl pyrrolidone were dissolved. In this solution, Compound A was dissolved and the solution was filtered through a 0.22 μm membrane filter, adjusted at pH 5.0 with hydrochloric acid, whereby precipitating a fine crystal (2 to 3 μm) of Compound A. Sodium alginate and tyloxapol were dissolved, and purified water was added to make the entire volume 100 mL, whereby obtaining an eye drop formulation as an aqueous suspension.

EXAMPLE 8

An eye drop formulation as an aqueous suspension was prepared using the following composition.

Component	Quantity
Compound A	1.0 g
Sodium citrate	0.1 g

Concentrated glycerin	1.2 g
Benzalkonium chloride	0.005 g
Polyvinyl pyrrolidone (K-25)	0.5 g
Sodium alginate	0.2 g
Tyloxapol	0.1 g
Hydrochloric acid	As appropriate
Sterilized purified water	to 100 mL (pH 5.0)

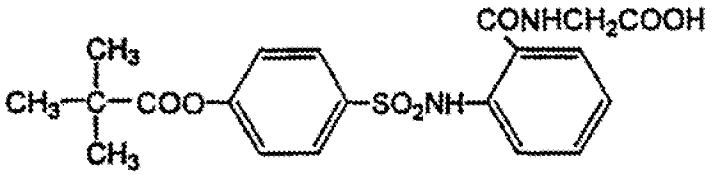
In about 80 ml of purified water, sodium citrate, concentrated glycerin and polyvinyl pyrrolidone were dissolved. In this solution, Compound A was dissolved and the solution was filtered through a 0.22 μm membrane filter, adjusted at pH 5.0 with hydrochloric acid, whereby precipitating a fine crystal (2 to 3 μm) of Compound A. Sodium alginate and tyloxapol were dissolved, and then benzalkonium chloride was dissolved. Purified water was added to make the entire volume 100 mL, whereby obtaining an eye drop formulation as an aqueous suspension.

INDUSTRIAL APPLICABILITY

According to the present invention, the pharmaceutical or a veterinary medicine which is effective in preventing or treating ophthalmic diseases, especially ophthalmic inflammatory diseases and corneal ulcer, can be provided.

What is claimed is:

1. A prophylactic and therapeutic medicament for ophthalmic diseases comprising as an active ingredient a compound represented by the formula (I):



(I)

or a pharmacologically acceptable salt or hydrate thereof.

2. The prophylactic and therapeutic medicament according to Claim 1, wherein the active ingredient is N-[o-(p-pivaloyloxybenzenesulfonylamino)benzoyl]glycine monosodium salt tetrahydrate.

3. The prophylactic and therapeutic medicament according to Claim 1 which is in a dosage form for local administration.

4. The prophylactic and therapeutic medicament according to Claim 3 which is an eye drop formulation.

5. The prophylactic and therapeutic medicament according to Claim 4 which is an eye drop formulation in the form of an aqueous suspension.

6. The prophylactic and therapeutic medicament according to Claim 3 which is an ophthalmic ointment.

7. The prophylactic and therapeutic medicament

according to Claim 1 which is in a prophylactic and therapeutic medicament for ophthalmic inflammatory diseases.

8. The prophylactic and therapeutic medicament according to Claim 7 which is in a prophylactic and therapeutic medicament for keratoconjunctival inflammatory diseases.

9. The prophylactic and therapeutic medicament according to Claim 1 which is in a prophylactic and therapeutic medicament for corneal ulcer.

10. The prophylactic and therapeutic medicament according to Claim 9 which is in a prophylactic and therapeutic medicament for infectious corneal ulcer.

11. The prophylactic and therapeutic medicament according to any one of Claims 1 to 10 which is used together with at least one of antibiotics, antibacterial agents, antiviral agents and antimycotic agents.

12. A method for preventing and treating ophthalmic diseases which comprises administering an effective amount of a compound represented by the formula (I) or a pharmacologically acceptable salt or hydrate thereof to a mammal in need of a treatment for such ophthalmic disease.

13. The method according to Claim 12, wherein N-

[o-(p-pivaloyloxybenzenesulfonylamino)benzoyl]glycine monosodium salt tetrahydrate is administered.

14. The method according to Claim 12, wherein the ophthalmic disease is an ophthalmic inflammatory disease.

15. The method according to Claim 14, wherein the ophthalmic inflammatory disease is a keratoconjunctival inflammatory disease.

16. The method according to Claim 12, wherein the ophthalmic disease is corneal ulcer.

17. The method according to Claim 16, wherein the corneal ulcer is an infectious corneal ulcer.

18. The method according to Claim 12, wherein at least one of antibiotics, antibacterial agents, antiviral agents and antimycotic agents is used together.

19. Use of a compound represented by the formula (I) or a pharmacologically acceptable salt or hydrate thereof in the manufacture of a prophylactic and therapeutic medicament for ophthalmic diseases.

20. Use according to Claim 19, wherein N-[o-(p-pivaloyloxybenzenesulfonylamino)benzoyl]glycine monosodium salt tetrahydrate is used.

21. Use according to Claim 19, wherein the ophthalmic disease is an ophthalmic inflammatory

disease.

22. Use according to Claim 21, wherein the ophthalmic inflammatory disease is a keratoconjunctival inflammatory disease.

23. Use according to Claim 19, wherein the ophthalmic disease is a corneal ulcer.

24. Use according to Claim 23, wherein the corneal ulcer is an infectious corneal ulcer.

25. Use according to Claim 19, wherein at least one of antibiotics, antibacterial agents, antiviral agents and antimycotic agents is used together.

26. An eye drop formulation in the form of an aqueous suspension of a compound represented by the formula (I) or a pharmacologically acceptable salt or hydrate thereof which is adjusted at pH 4 to 5.5 using at least one pH modifier.

27. The eye drop formulation in the form of an aqueous suspension according to Claim 26, wherein the pH modifier is hydrochloric acid or hydrochloric acid in combination with sodium hydroxide.

28. The eye drop formulation in the form of an aqueous suspension according to Claim 26 comprising a buffering agent, an isotonicity, a suspending agent and a dispersing agent.

29. The eye drop formulation in the form of an

aqueous suspension according to Claim 28, wherein the buffering agent is sodium citrate or sodium acetate.

30. The eye drop formulation in the form of an aqueous suspension according to Claim 28, wherein the isotonicity is concentrated glycerin and/or propylene glycol.

31. The eye drop formulation in the form of an aqueous suspension according to Claim 28, wherein the suspending agent is polyvinyl pyrrolidone.

32. An eye drop formulation in the form of an aqueous suspension according to Claim 28, wherein the dispersing agent is a surfactant and/or sodium alginate.

33. The eye drop formulation in the form of an aqueous suspension according to the above-mentioned Claim 32 wherein the surfactant is tyloxapol or polysorbate 80.

Fig. 1

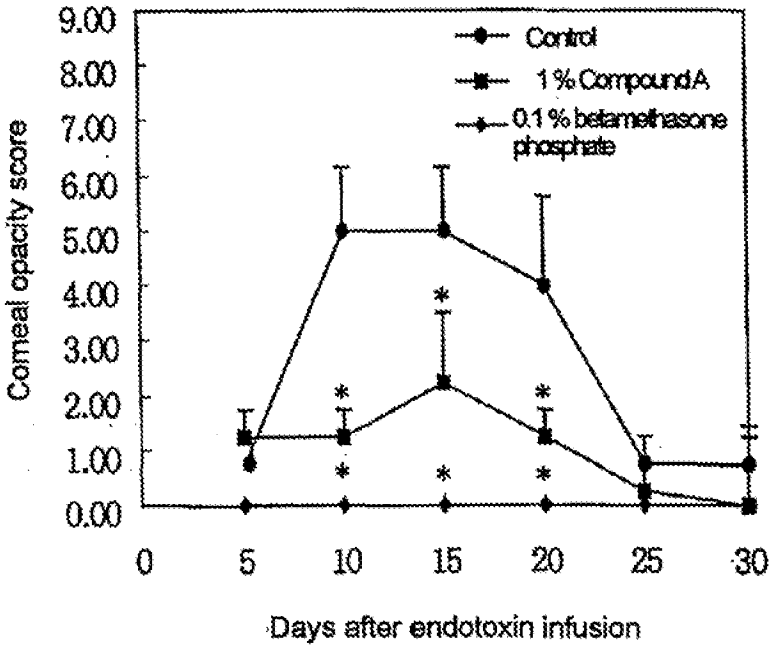

9.00
8.00
7.00
6.00
5.00
4.00
3.00
2.00
1.00
0.00
Corneal opacity score
Control
1% Compound A
0.1% betamethasone phosphate
*
0
5
10
15
20
25
30
Days after endotoxin infusion

Fig. 2

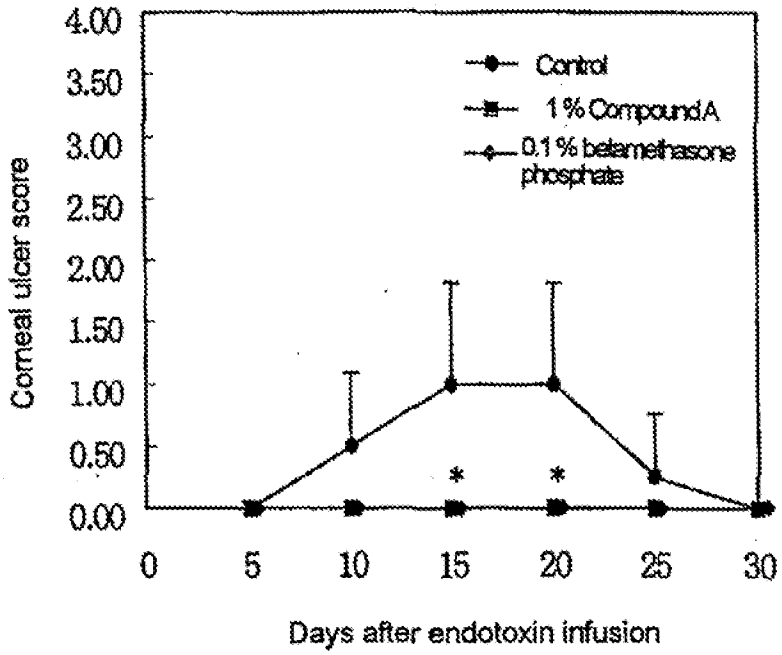

4.00
3.50
3.00
2.50
2.00
1.50
1.00
0.50
0.00
Corneal ulcer score
Control
1% CompoundA
0.1% betamethasone phosphate
*
*
0
5
10
15
20
25
30
Days after endotoxin infusion

Fig. 3

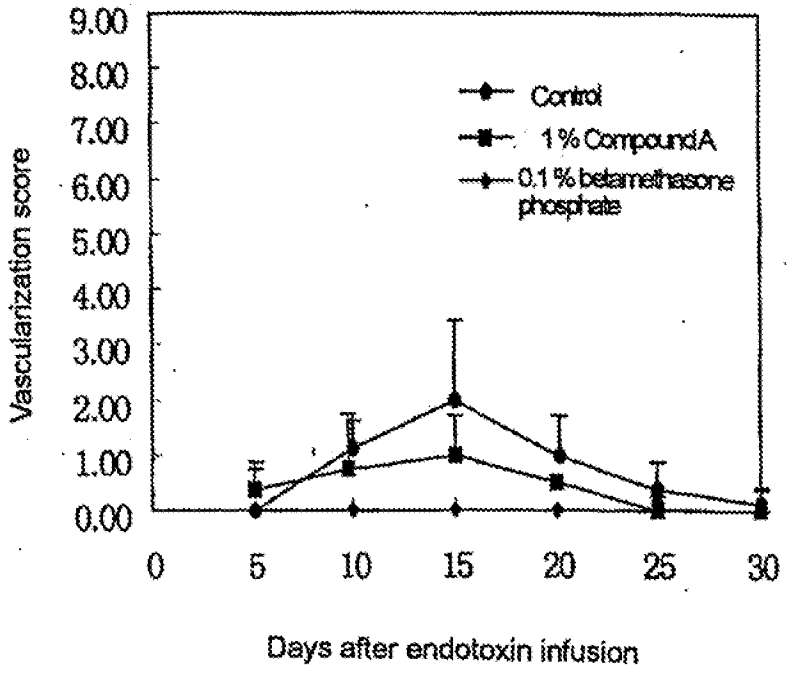

9.00
8.00
7.00
6.00
5.00
4.00
3.00
2.00
1.00
0.00
Vascularization score
Control
1% CompoundA
0.1% betamethasone phosphate
0
5
10
15
20
25
30
Days after endotoxin infusion

Fig. 4

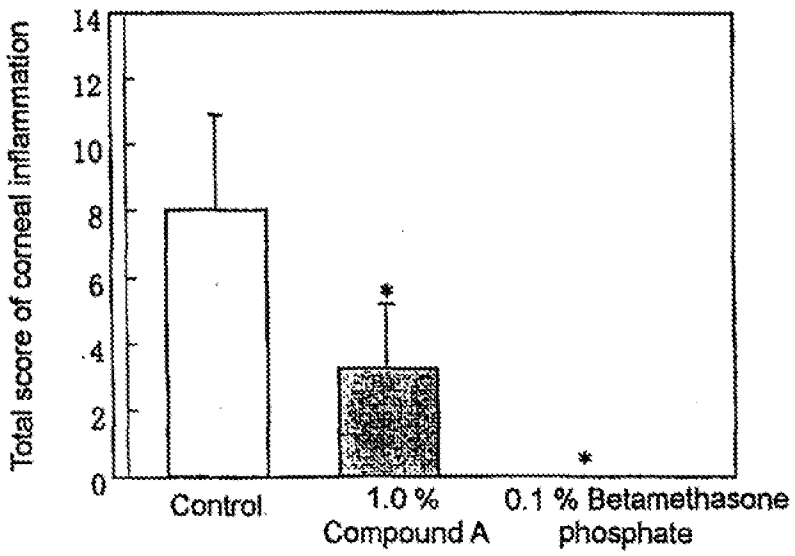

Total score of corneal inflammation
14
12
10
8
6
4
2
0
*
*
Control
1.0 %
Compound A
0.1 % Betamethasone
phosphate

Fig. 5

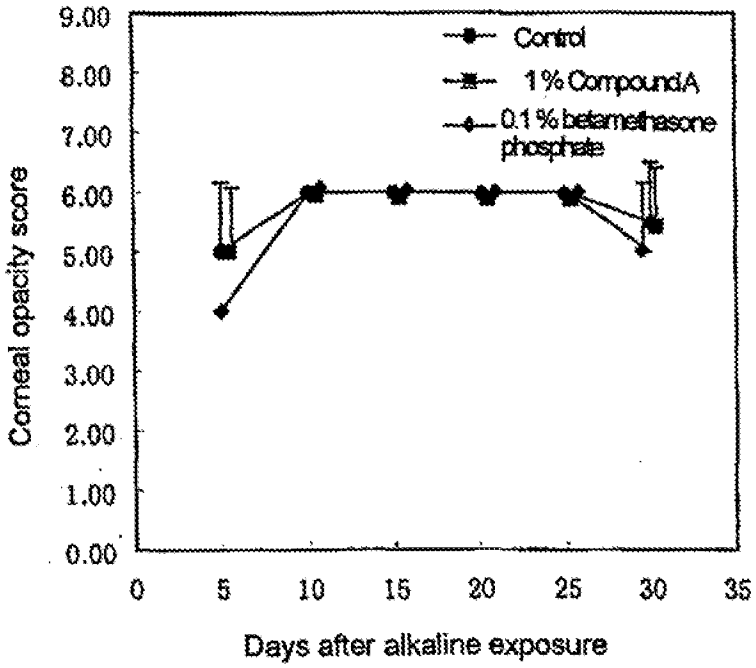

9.00
8.00
7.00
6.00
5.00
4.00
3.00
2.00
1.00
0.00
Corneal opacity score
0
5
10
15
20
25
30
35
Days after alkaline exposure
Control
1% CompoundA
0.1% betamethasone phosphate

Fig. 6

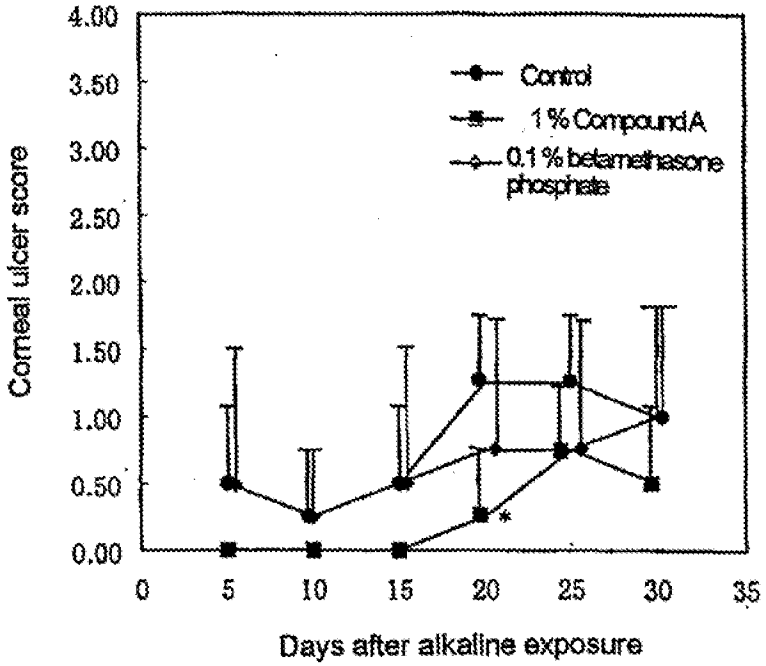

4.00
3.50
3.00
2.50
2.00
1.50
1.00
0.50
0.00
Corneal ulcer score
Control
1% Compound A
0.1% betamethasone phosphate
*
0
5
10
15
20
25
30
35
Days after alkaline exposure

Fig. 7

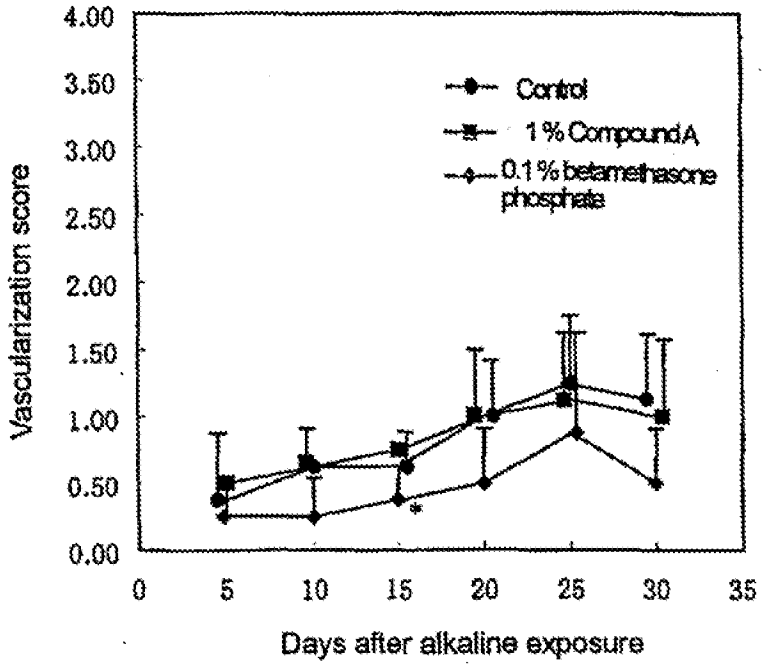

4.00
3.50
3.00
2.50
2.00
1.50
1.00
0.50
0.00
Vascularization score
Control
1% Compound A
0.1% betamethasone phosphate
*
0
5
10
15
20
25
30
35
Days after alkaline exposure

Fig. 8

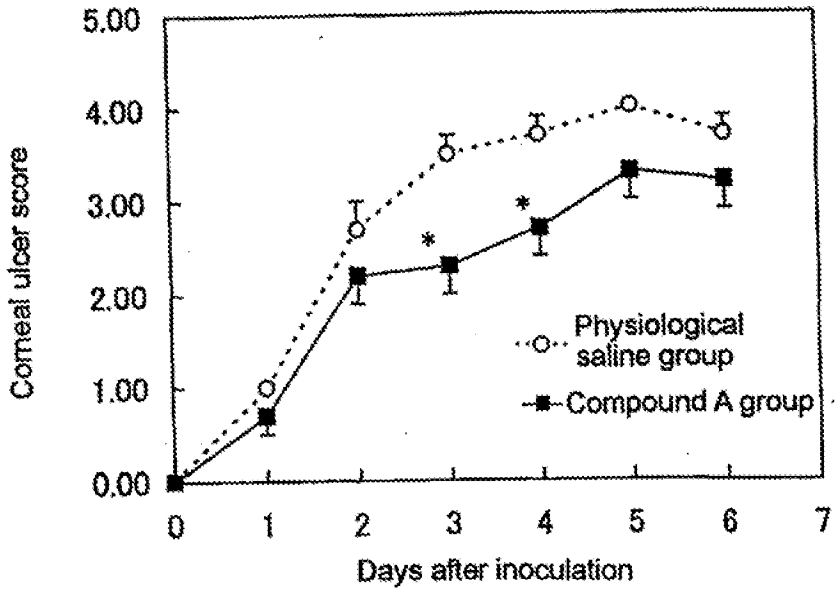
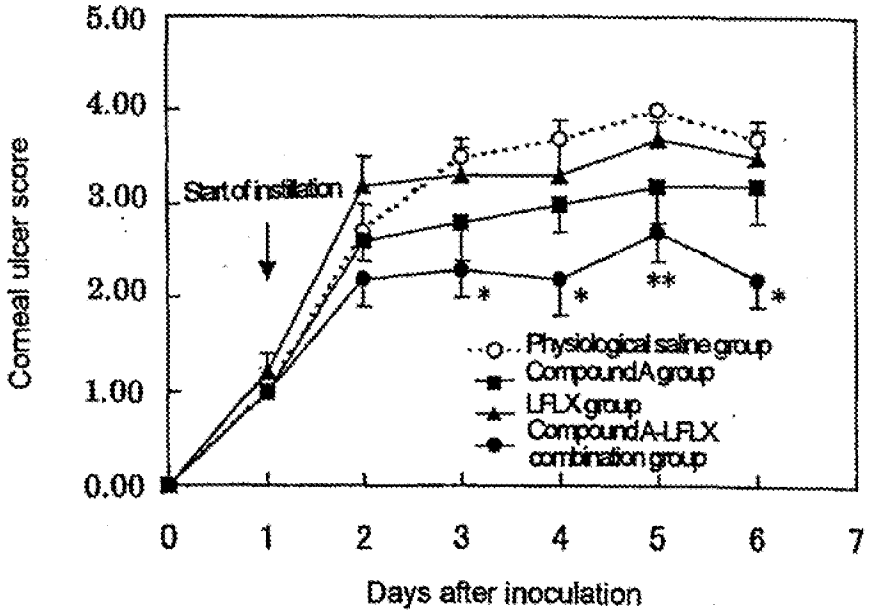

5.00
4.00
3.00
2.00
1.00
0.00
Corneal ulcer score
0
1
2
3
4
5
6
7
Days after inoculation
Physiological saline group
Compound A group
*
*

Fig. 9


5.00
4.00
3.00
2.00
1.00
0.00
Corneal ulcer score
Start of instillation
*
*
**
*
Physiological saline group
Compound A group
LFLX group
Compound A-LFLX combination group
0
1
2
3
4
5
6
7
Days after inoculation

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(54) Title: METHOD OF TREATING ANGIOGENESIS-RELATED DISORDERS

(57) Abstract: The use of 3-benzolphenylacetic acids and derivatives, including nepafenac, to treat angiogenesis-related disorders, including ophthalmic angiogenesis-related disorders such as diabetic retinopathy and exudative macular degeneration, is disclosed.

METHOD OF TREATING ANGIOGENESIS-RELATED DISORDERS

FIELD OF THE INVENTION

This invention relates to the use of certain 3-benzoylphenylacetic acids and derivatives to treat or prevent angiogenic diseases.

BACKGROUND OF THE INVENTION

3-benzoylphenylacetic acid and certain of its derivatives are known to possess anti-inflammatory activity. U.S. Patent Nos. 4,254,146, 4,045,576, 4,126,635, and 4,503,073, and U.K. Patent Application Nos. 2,071,086A and 2,093,027A disclose various 3-benzoylphenylacetic acids, salts and esters, and hydrates thereof, having anti-inflammatory activity. U.S. Patent No. 4,568,695 discloses 2-amino-3-benzoylphenylethyl alcohols having anti-inflammatory activity. U.S. Patent No. 4,313,949 discloses 2-amino-3-benzoyl-phenylacetamides having anti-inflammatory activity.

Certain derivatives of 2-amino-3-benzoylbenzeneacetic acid (amfenac) and 2-amino-3-(4-chloro-benzoyl)benzeneacetic acid have also been evaluated by Walsh et al., J. Med Chem., 33:2296-2304 (1990), in an attempt to discover nonsteroidal anti-inflammatory prodrugs with minimal or no gastrointestinal side effects upon oral administration.

U.S. patent No. 4,683,242 teaches the transdermal administration of 2-amino-3-benzoylphenylacetic acids, salts, and esters, and hydrates and alcoholates thereof to control inflammation and alleviate pain.

U.S. Patent No. 4,910,225 teaches certain benzoylphenylacetic acids for local administration to control ophthalmic, nasal or otic inflammation. Only acetic acids are disclosed in the '225 patent; no esters or amides are

mentioned or taught as anti-inflammatory agents for local administration to the eyes, nose and ears.

U.S. Patent No. 5,475,034 discloses topically administrable compositions containing certain amide and ester derivatives of 3-benzyolphenylacetic acid, including nepafenac, useful for treating ophthalmic inflammatory disorders and ocular pain. According to the '035 patent at Col. 15, lines 35-39, "[s]uch disorders include, but are not limited to uveitis scleritis, *episcleritis, keratitis, surgically-induced inflammation and endophthalmitis.*"

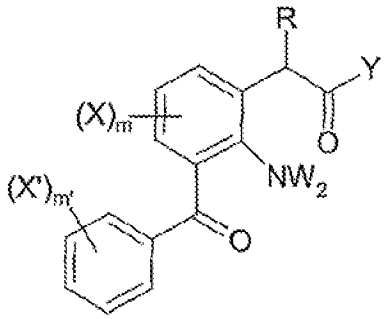
U.S. Patent No. 6,066,671 discloses the topical use of certain amide and ester derivatives of 3-benzoylphenylacetic acid, including nepafenac, for treating GLC1A glaucoma.

SUMMARY OF THE INVENTION

It has now been found that certain 3-benzoylphenlacetic acids and derivatives, including nepafenac (2-amino,3-benzoyl-phenylacetamide), are useful for the treatment of angiogenesis-related disorders.

DETAILED DESCRIPTION OF THE INVENTION

The 3-benzoylphenylacetic acids and derivatives useful in the methods of the present invention are those of formula (I) below.



(I)

R = H, C_{1-4} (un)branched alkyl, CF_3, SR^4;

Y = OR', NR"R';

R' = H, C_{1-10} (un)branched alkyl, (un)substituted (substitution as defined by X below), (un)substituted heterocycle (substitution as defined by X below), $-(CH_2)_nZ(CH_2)_{n'}A$;

n = 2-6;

n'= 1-6;

Z = nothing, O, C=O, OC(=O), C(=O)O, $C(=O)NR^3$, $NR^3C(=O)$, $S(O)_{n2}$, $CHOR^3$, NR^3;

n^2 = 0-2;

R^3 = H, C_{1-6} (un)branched alkyl, (un)substituted aryl (substitution as defined by X below), (un)substituted heterocycle (substitution as defined by X below);

A = H, OH, optionally (un)substituted aryl (substitution as defined by X below), (un)substituted heterocycle (substitution as defined by X below), $-(CH_2)_nOR^3$;

R" = H, OH, OR';

X and X' independently = H, F, Cl, Br, I, OR', CN, OH, $S(O)_{n2}R^4$, CF_3, R^4, NO_2;

R^4 = C_{1-6} (un)branched alkyl;

m = 0-3;

m' = 0-5;

W = O, H.

As used herein, the acid (Y = OH) includes pharmaceutically acceptable salts as well.

Preferred compounds for use in the methods of the present invention are those of Formula I wherein:

R = H, C_{1-2} alkyl;
Y = NR'R";
R' = H, C_{1-6} (un)branched alkyl, —$(CH_2)_m$Z$(CH_2)_{n'}$A;
Z = nothing, O, $CHOR^3$, NR^3;
R_3 = H;
A = H, OH, (un)substituted aryl (substitution as defined by X below);
X and X' independently = H, F, Cl, Br, CN, CF_3, OR', SR^4, R^4;
R" = H;
R^4 = C_{1-4} (un)branched alkyl;
m = 0-2;
m' = 0-2;
W = H;
n = 2-4;
n' = 0-3.

The most preferred compounds for use in the compositions or method of the present invention are 2-Amino-3-(4-fluorobenzoyl)-phenylacetamide; 2-Amino-3-benzoyl-phenylacetamide (nepafenac); and 2-Amino-3-(4-chlorobenzoyl)-phenylacetamide.

According to the present invention, a therapeutically effective amount of a compound of formula (I) is administered topically, locally or systemically to treat or prevent angiogenesis-related disorders. Such disorders include those that involve the proliferation of tumor cells, such as prostate cancer, lung cancer, breast cancer, bladder cancer, renal cancer, colon cancer, gastric cancer, pancreatic cancer, ovarian cancer, melanoma, hepatoma, sarcoma and lymphoma. Ophthalmic angiogenesis-related disorders include, but are not limited to exudative macular degeneration; proliferative diabetic retinopathy; ischemic retinopathy (e.g., retinal vein or artery occlusion); retinopathy of

prematurity; neovascular glaucoma; iritis rubeosis; corneal neovascularization; cyclitis; sickle cell retinopathy; and pterygium. Certain disorders, such as sickle cell retinopathy and retinal vein or artery occlusion, can be characterized by both angiogenesis and neurodegenerative components. According to the present invention, a compound of formula (I) is administered to treat or prevent disorders characterized, at least in part, by angiogenesis.

The compounds of formula (I) can be administered in a variety of ways, including all forms of local delivery to the eye, such as subconjunctival injections or implants, intravitreal injections or implants, sub-Tenon's injections or implants, incorporation in surgical irrigating solutions, etc. Additionally, the compounds of formula (I) can be administered systemically, such as orally or intravenously. Suitable pharmaceutical vehicles or dosage forms for injectable compositions, implants, and systemic administration are known. The compounds of formula (I) and especially those wherein Y = NR'R", however, are preferably administered topically to the eye and can be formulated into a variety of topically administrable ophthalmic compositions, such as solutions, suspensions, gels or ointment.

Pharmaceutical compositions comprising a compound of formula (I) in aqueous solution or suspension, optionally containing a preservative for multidose use and other conventionally employed ophthalmic adjuvants, can be topically administered to the eye. The most preferred form of delivery is by aqueous eye drops, but gels or ointments can also be used. Aqueous eye drops, gels and ointments can be formulated according to conventional technology and would include one or more excipients. For example, topically administrable compositions may contain tonicity-adjusting agents, such as mannitol or sodium chloride; preservatives such as chlorobutanol, benzalkonium chloride, polyquaternium-1, or chlorhexidine; buffering agents, such as phosphates, borates, carbonates and citrates; and thickening agents, such as high molecular weight carboxy vinyl polymers, including those known as carbomers, hydroxyethylcellulose, or polyvinyl alcohol.

The doses of the compounds of formula (I) used in the treatment or prevention of ophthalmic angiogenesis-related disorders will depend on the type of disorder to be prevented or treated, the age and body weight of the patient, and the form of preparation/route of administration. Compositions intended for topical ophthalmic administration will typically contain a compound of formula (I) in an amount of from about 0.001 to about 4.0% (w/v), preferably from about 0.01 to about 0.5% (w/v), with 1-2 drops once to several times a day. Likewise, representative doses for other forms of preparations are approximately 1 – 100 mg/day/adult for injections and approximately 10 – 1000 mg/adult for oral preparations, each administered once to several times a day.

Additional therapeutic agents may be added to supplement the compounds of formula (I).

The following examples are presented to illustrate various aspects of the present invention, but are not intended to limit the scope of the invention in any respect. The percentages are expressed on a weight/volume basis.

Example 1: The following formulations are representative of the topical compositions useful in the present invention.

Formulation 1

Compound of formula (I)	0.01 – 0.5%
Polysorbate 80	0.01%
Benzalkonium Chloride	0.01% + 10% excess
Disodium EDTA	0.1%
Monobasic Sodium Phosphate	0.03%
Dibasic Sodium Phosphate	0.1%
Sodium Chloride	q.s. 290-300 mOsm/Kg
pH adjustment with NaOH and/or HCl	pH 4.2 – 7.4
Water	q.s. 100%

Formulation 2

Compound of formula (I)	0.01 – 0.5%
Hydroxypropyl Methylcellulose	0.5%
Polysorbate 80	0.01%
Benzalkonium Chloride	0.01% + 5% excess
Disodium EDTA	0.01%
Dibasic Sodium Phosphate	0.2%
Sodium Chloride	q.s. 290-300 mOsm/Kg
pH adjustment with NaOH and/or HCl	pH 4.2 – 7.4
Water	q.s. 100%

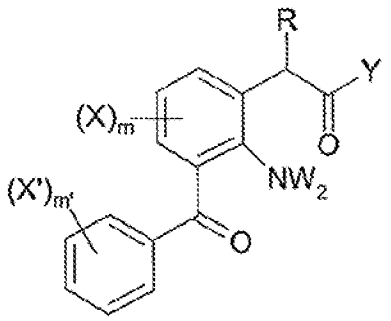
Formulation 3

Nepafenac	0.1 + 6% excess
Carbopol 974P	0.08%
Tyloxapol	0.01%
Glycerin	2.4%
Disodium EDTA	0.01%
Benzalkonium Chloride	0.01%
pH adjustment with NaOH and/or HCl	pH 7.5 ± 0.2
Water	q.s. 100%

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

We Claim:

1. A method of treating or preventing an angiogenesis-related disorder in a patient suffering from or predisposed to such a disorder which comprises administering to the patient a therapeutically effective amount of 3-benzoylphenylacetic acid or derivative of the formula:



wherein

R = H, C_{1-4} (un)branched alkyl, CF_3, SR^4;

Y = OR', NR"R';

R' = H, C_{1-10} (un)branched alkyl, (un)substituted (substitution as defined by X below), (un)substituted heterocycle (substitution as defined by X below), $-(CH_2)_nZ(CH_2)_nA$;

n = 2-6;

n'= 1-6;

Z = nothing, O, C=O, OC(=O), C(=O)O, $C(=O)NR^3$, $NR^3C(=O)$, $S(O)_{n2}$, $CHOR^3$, NR^3;

n^2 = 0-2;

R^3 = H, C_{1-6} (un)branched alkyl, (un)substituted aryl (substitution as defined by X below), (un)substituted heterocycle (substitution as defined by X below);

A = H, OH, optionally (un)substituted aryl (substitution as defined by X below), (un)substituted heterocycle (substitution as defined by X below), $-(CH_2)_nOR^3$;

R" = H, OH, OR';

X and X' independently = H, F, Cl, Br, I, OR', CN, OH, $S(O)_{n2}R^4$, CF_3, R^4, NO_2;