UNITED STATES PATENT AND TRADEMARK OFFICE

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APPLICATION NO.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/353,653	07/30/2013	8497304	2012_0088	1077

513 7590 07/10/2013

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, Kobe-shi, JAPAN;
Shuhei Fujita, Kakogawa, 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 06/07/2013
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.
13/353,653	01/19/2012	Shirou Sawa	2012_0088	1077

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	$1780	$300	$0	$2080	09/09/2013

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 credit 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

NOTE: Absent a valid certification of Micro Entity Status (see form 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: The Issue Fee and Publication Fee (if required) will not be accepted from anyone other than the applicant; a registered attorney or agent; or the assignee or other party in interest as shown by the records of the United States Patent and Trademark Office.

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: 2013.06.26 13:30:36 -04'00' Date June 26, 2013

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

This collection of information 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.

Electronic Patent Application Fee Transmittal

Application Number:	13353653
Filing Date:	19-Jan-2012
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:	2012_0088

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	1780	1780
Publ. Fee- Early, Voluntary, or Normal	1504	1	300	300

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Miscellaneous:				
			Total in USD ($)	**2080**

Electronic Acknowledgement Receipt

EFS ID:	16160479
Application Number:	13353653
International Application Number:	
Confirmation Number:	1077
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./ANN LEVEILLE
Filer Authorized By:	Warren M. Cheek Jr.
Attorney Docket Number:	2012_0088
Receipt Date:	26-JUN-2013
Filing Date:	19-JAN-2012
Time Stamp:	15:52:34
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Credit Card
Payment was successfully received in RAM	$2080
RAM confirmation Number	2800
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	484473 ed745934b56b87a273a9c7c615d0c4eb50e06cf9	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:

2	Fee Worksheet (SB06)	fee-info.pdf	32721 5fe147f5a432a6d9687baa06de349fdce208139d	no	2

Warnings:

Information:

Total Files Size (in bytes):	517194

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.

UNITED STATES PATENT AND TRADEMARK OFFICE

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www.uspto.gov

NOTICE OF ALLOWANCE AND FEE(S) DUE

513 7590 06/07/2013

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: 06/07/2013

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/353,653	01/19/2012	Shirou Sawa	2012_0088	1077

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	$1780	$300	$0	$2080	09/09/2013

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

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

513 7590 06/07/2013
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.
13/353,653	01/19/2012	Shirou Sawa	2012_0088	1077

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	$1780	$300	$0	$2080	09/09/2013

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 credit 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 form 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: The Issue Fee and Publication Fee (if required) will not be accepted from anyone other than the applicant; a registered attorney or agent; or the assignee or other party in interest as shown by the records of the United States Patent and Trademark Office.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

This collection of information 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.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/353,653	01/19/2012	Shirou Sawa	2012_0088	1077

513 7590 06/07/2013

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: 06/07/2013

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

The Patent Term Adjustment to date is 0 day(s). If the issue fee is paid on the date that is three months after the mailing date of this notice and the patent issues on the Tuesday before the date that is 28 weeks (six and a half months) after the mailing date of this notice, the Patent Term Adjustment will be 0 day(s).

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 Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

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)	
	13/353,653	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 amendments made on 5/20/13*.

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 *1,8,9,11-14 and 16-25*.

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 _____
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 *5/21/13* .
7. ☐ Examiner's Amendment/Comment
8. ☒ Examiner's Statement of Reasons for Allowance
9. ☐ Other _____.

Examiner-Initiated Interview Summary	Application No.	Applicant(s)	
	13/353,653	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: *30 April 2013*.

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. The Attoreny of record needed time to consult with Applicant. However, in a written response the Appropriate amendments were made to the claims to overcome the rejections .

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

/Layla Soroush/ Examiner, Art Unit 1627	

Acknowledgement of Receipt

Applicant's response filed on 05/20/2013 to the Office Action mailed on 05/10/2013 is acknowledged.

Claim Status

Claims 1, 8-9, 11-14, 16-25 are pending.

Claims 1, 8-9, 11-14, 16-25 are allowed.

Withdrawn Rejections

The rejection of claims 1, 4-5, 8, 19-20, 22, and 28 under 35 U.S.C. 103(a) as being unpatentable over Chen et al. (US 6383471), as applied to claims above, and further in view of Fukahori et al. (JP 402083323A) is withdrawn in view of the amendments made to the claims.

The rejection of claims 1, 4-5, 9, 11-14, 19-22, and 28 under 35 U.S.C. 103(a) as being unpatentable over Sawa (5942508) in view of Chen et al. (US 6383471), and further in view of Fukahori et al. (JP 402083323A) is withdrawn in view of the amendments made to the claims.

The rejection of claims 1, 4-5, 8-9, 11-14, 19-22, and 28 under 35 U.S.C. 103(a) as being unpatentable over Sawa (6274592) in view of Chen et al. (US 6383471), as applied to claims and further in view of Fukahori et al. (JP 402083323A) is withdrawn in view of the amendments made to the claims.

The rejection of claims 1, 4-5, 8, 13, 19-20, 22, and 28 under 35 U.S.C. 103(a) as being unpatentable over Sawa (20010056098) in view of Chen et al. (US 6383471), as

applied to claims further in view of Fukahori et al. (JP 402083323A) is withdrawn in view of the amendments made to the claims.

The rejection of claims 9, 11- 14, and 21 under 35 U.S.C. 103(a) as being unpatentable over Chen et al. (US 6383471) and Fukahori et al. (JP 402083323A), as applied to claims 1, 4-5, 8, 19-20, 22, and 28 above, and further in view of Sawa (5942508) is withdrawn in view of the amendments made to the claims.

The rejection of claims 9, 11-14, and 21 under 35 U.S.C. 103(a) as being unpatentable over Chen et al. (US 6383471) and Fukahori et al. (JP 402083323A), as applied to 1, 4-5, 8, 19-20, 22, and 28 above, and further in view of Sawa (6274592) is withdrawn in view of the amendments made to the claims.

The rejection of claims 9, 11-14, and 21 under 35 U.S.C. 103(a) as being unpatentable over Chen et al. (US 6383471) and Fukahori et al. (JP 402083323A), as applied to claims 1, 4-5, 8, 19-20, 22, and 28 above, and further in view of Sawa (20010056098) is withdrawn in view of the amendments made to the claims.

The rejection of claims 9, 21, and 23 under 35 U.S.C. 103(a) as being unpatentable over Chen et al. (US 6383471) and Fukahori et al. (JP 402083323A), as applied to claims 1, 4-5, 8, 19-20, 22, and 28 above, and further in view of Gamache et al. (WO 01/15677) and Yakuji Nippo Ltd., ("New Drugs in Japan: 2001", 2001 Edition, Published by May 11, 2001, p.27-29 - IDS) is withdrawn in view of the amendments made to the claims.

The rejection of claims 10, and 23-25 under 35 U.S.C. 103(a) as being unpatentable over Sawa (5942508) in view of Chen et al. (US 6383471) and Fukahori et

al. (JP 402083323A), as applied to claims 1, 4-5, 9, 11-14, 19-22, and 28 above, and further in view of Gamache et al. (WO 01/15677) and Yakuji Nippo Ltd., ("New Drugs in Japan: 2001", 2001 Edition, Published by May 11, 2001, p.27-29 - IDS) is withdrawn in view of the amendments made to the claims.

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The rejection of claim 16 under 35 U.S.C. 103(a) as being unpatentable over Sawa (20010056098) in view of Chen et al. (US 6383471) and Fukahori et al. (JP 402083323A), as applied to claims 1, 4-5, 8, 19-20, 22, and 28 above, and further in view of Aikawa et al. (JP 2002308764 A) is withdrawn in view of the amendments made to the claims.

The rejection of claim 16 under 35 U.S.C. 103(a) as being unpatentable over Sawa (5942508) in view of Chen et al. (US 6383471) and Fukahori et al. (JP 402083323A), as applied to claims 1, 4-5, 9, 11-14, 19-22, and 28 above, and further in view of Aikawa et al. (JP 2002308764 A) is withdrawn in view of the amendments made to the claims.

The rejection of claim 16 under 35 U.S.C. 103(a) as being unpatentable over Sawa (6274592) in view of Chen et al. (US 6383471) and Fukahori et al. (JP 402083323A), as applied to claims 1, 4-5, 8-9, 11-14, 19-22, and 28 above, and further in view of Aikawa et al. (JP 2002308764 A) is withdrawn in view of the amendments made to the claims.

The rejection of claim 16 under 35 U.S.C. 103(a) as being unpatentable over over Sawa (20010056098) in view of Chen et al. (US 6383471) and Fukahori et al. (JP 402083323A), as applied to claims 1, 4-5, 8, 13, 19-20, 22, and 28 above, and further in view of Aikawa et al. (JP 2002308764 A) is withdrawn in view of the amendments made to the claims.

The Double Patenting rejections over U.S. Patent No. 7829544, U.S. Patent No. 5942508, copending Application No. 11755662 is withdrawn in view of the amendments made to the claims.

Reasons for Allowance

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

The composition and method as claimed are found to be patentable over the prior art because the prior art does not teach or fairly suggest an aqueous liquid

preparation comprising 2-amino-3-(4- bromobenzoyl)phenylacetic acid sodium salt thereof or a hydrate thereof, and polyoxyl 40 stearate, wherein the concentration of the polyethylene glycol fatty acid ester is selected from a range of a minimum concentration of 0.02 w/v % to a maximum concentration of 0.1 w/v%.

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 on the basis of the specific combination of limitations (1) to (4), the present invention shows excellent effects in that (1) the aqueous liquid preparation is stable within a pH range giving no irritation to eyes; and (2) the change of the 2-amino-3- (4-bromobenzoyl) phenylacetic acid over time can be inhibited, (c.f. page 4, lines 11-14 of the specification). These excellent effects are

clearly demonstrated by Experiments 1 to 3 of Rule 1.132 Declaration executed by Mr. Shirou Sawa. Experiments 1 to 3 of Rule 1.132 Declaration respectively correspond to Experimental Examples 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 arguments are persuasive.

The method as claimed are found to be patentable over the prior art because the prior art does not teach or fairly suggest an aqueous liquid preparation comprising 2-amino-3-(4- bromobenzoyl)phenylacetic acid sodium salt thereof or a hydrate thereof, and polyoxyl 40 stearate, wherein the concentration of the polyethylene glycol fatty acid ester is selected from a range of a minimum concentration of 0.02 w/v % to a maximum concentration of 0.1 w/v%.

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

Search Notes	Application/Control No.	Applicant(s)/Patent under Reexamination	
	13/353,653	SAWA ET AL.	
	Examiner	Art Unit	
	LAYLA SOROUSH	1627	

SEARCHED			
Class	Subclass	Date	Examiner
514	619	5/1/13	LS
514	535	5/1/13	LS
514	570	5/1/13	LS

INTERFERENCE SEARCHED			
Class	Subclass	Date	Examiner
514	**618**	**5/1/13**	**LS**

SEARCH NOTES (INCLUDING SEARCH STRATEGY)		
	DATE	EXMR
STIC: npl and pat	5/1/13	LS
odp:SAWA, SHIROU and FUJITA, SHUHEI	5/21/13	LS

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Named Inventor	:	Attorney Docket No. 2012-0088
Shirou SAWA	:	**Confirmation No. 1077**
Serial No. 13/353,653	:	Group Art Unit 1627
Filed January 19, 2012	:	Examiner Layla Soroush
AQUEOUS LIQUID PREPARATION CONTAINING 2-AMINO-3-(4-BROMOBENZOYL)PHENYLACETIC ACID	:	**Mail Stop: AF**

OK TO ENTER: /L.S./

AMENDMENT

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

Sir/Madam:

Responsive to the Official Action dated May 10, 2013, please amend the above-identified application as follows:

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.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

BIB DATA SHEET

CONFIRMATION NO. 1077

SERIAL NUMBER	FILING or 371(c) DATE RULE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
13/353,653	01/19/2012	514	1627	2012_0088

APPLICANTS

Shirou Sawa, Kobe-shi, JAPAN;
Shuhei Fujita, Kakogawa, JAPAN;

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

This application 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 ****

01/31/2012

Foreign Priority claimed ☑ Yes ☐ No 35 USC 119(a-d) conditions met ☑ Yes ☐ No Verified and Acknowledged /LAYLA SOROUSH/ Examiner's Signature	☑ Met after Allowance LS Initials	STATE OR COUNTRY	SHEETS DRAWINGS	TOTAL CLAIMS	INDEPENDENT CLAIMS
		JAPAN	0	18	5

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		
2050	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

Issue Classification	Application/Control No. 13/353,653	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/ 5/21/13 (Primary Examiner) (Date)	Total Claims Allowed: 17	
(Legal Instruments 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	1		31		61		91		121		151		181
	2		32		62		92		122		152		182
	3		33		63		93		123		153		183
	4		34		64		94		124		154		184
	5		35		65		95		125		155		185
	6		36		66		96		126		156		186
	7		37		67		97		127		157		187
2	8		38		68		98		128		158		188
3	9		39		69		99		129		159		189
	10		40		70		100		130		160		190
4	11		41		71		101		131		161		191
5	12		42		72		102		132		162		192
6	13		43		73		103		133		163		193
7	14		44		74		104		134		164		194
	15		45		75		105		135		165		195
8	16		46		76		106		136		166		196
9	17		47		77		107		137		167		197
10	18		48		78		108		138		168		198
11	19		49		79		109		139		169		199
12	20		50		80		110		140		170		200
13	21		51		81		111		141		171		201
14	22		52		82		112		142		172		202
15	23		53		83		113		143		173		203
16	24		54		84		114		144		174		204
17	25		55		85		115		145		175		205
	26		56		86		116		146		176		206
	27		57		87		117		147		177		207
	28		58		88		118		148		178		208
	29		59		89		119		149		179		209
	30		60		90		120		150		180		210

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Named Inventor	:	Attorney Docket No. 2012-0088
Shirou SAWA	:	**Confirmation No. 1077**
Serial No. 13/353,653	:	Group Art Unit 1627
Filed January 19, 2012	:	Examiner Layla Soroush
AQUEOUS LIQUID PREPARATION CONTAINING 2-AMINO-3-(4-BROMOBENZOYL)PHENYLACETIC ACID	:	**Mail Stop: AF**

AMENDMENT

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

Sir/Madam:

Responsive to the Official Action dated May 10, 2013, please amend the above-identified application as follows:

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.

AMENDMENTS TO THE CLAIMS

1. (Currently amended) An aqueous liquid preparation comprising 2-amino-3-(4-bromobenzoyl)phenylacetic acid ~~or a~~ sodium salt ~~thereof~~ or a hydrate thereof, and ~~a polyethylene glycol fatty acid ester~~ polyoxyl 40 stearate,
wherein
the concentration of the ~~polyethylene glycol fatty acid ester~~ polyoxyl 40 stearate is selected from a range of a minimum concentration of 0.02 w/v % to a maximum concentration of 0.1 w/v%.

2-7. (Canceled)

8. (Currently amended) The aqueous liquid preparation according to claim 1, wherein the concentration of the 2-amino-3-(4-bromobenzoyl)phenylacetic acid ~~or the~~ sodium salt ~~thereof~~ or the hydrate thereof is 0.01 to 0.5 w/v %.

9. (Previously presented) The aqueous liquid preparation according to claim 1, wherein benzalkonium chloride is contained as a preservative.

10. (Canceled)

11. (Previously presented) The aqueous liquid preparation according to claim 1, wherein the pH of the aqueous liquid preparation is within a range of 7 to 9.

12. (Original) The aqueous liquid preparation according to claim 11, wherein the pH of the aqueous liquid preparation is within a range of 7.5 to 8.5.

13. (Previously presented) The aqueous liquid preparation according to claim 1, wherein the aqueous liquid preparation is an eye drop.

14. (Previously presented) The aqueous liquid preparation according to claim 1, wherein the aqueous liquid preparation is a nasal drop.

15. (Canceled)

16. (Currently amended) An eye drop comprising sodium 2-amino-3-(4-bromobenzoyl)phenylacetate hydrate and 0.02 to 0.1 w/v % of ~~polyethylene glycol monostearate~~ polyoxyl 40 stearate.

17. (Currently amended) A method for stabilizing 2-amino-3-(4-bromobenzoyl)phenylacetic acid ~~or a~~ sodium salt ~~thereof~~ or a hydrate thereof in an aqueous liquid preparation, which comprises incorporating ~~polyethylene glycol monostearate~~ polyoxyl 40 stearate into an aqueous liquid preparation containing 2-amino-3-(4-bromobenzoyl)phenylacetic acid ~~or a~~ sodium salt ~~thereof~~ or a hydrate thereof.

18. (Currently amended) A method for inhibiting decrease in preservative effect of a preservative in an aqueous liquid preparation of 2-amino-3-(4-bromobenzoyl)phenylacetic acid ~~or a~~ sodium salt ~~thereof~~ or a hydrate thereof, which comprises incorporating ~~tyloxapol or polyethylene glycol monostearate~~ polyoxyl 40 stearate into an aqueous liquid preparation containing 2-amino-3-(4-bromobenzoyl)phenylacetic acid ~~or a~~ sodium salt ~~thereof~~ or a hydrate thereof and a preservative.

19. (Currently amended) The aqueous liquid preparation according to claim 1, which consists essentially of the following two components, wherein the first component is the 2-amino-3-(4- bromobenzoyl)phenylacetic acid ~~or the~~ sodium salt ~~thereof~~ or the hydrate thereof, and the second component is ~~the polyethylene glycol fatty acid ester~~ polyoxyl 40 stearate.

20. (Previously presented) The aqueous liquid preparation according to claim 1, which is formulated for ophthalmic administration.

21. (Previously presented) The aqueous liquid preparation according to claim 1, wherein when a quaternary ammonium compound is included in said liquid preparation, the quaternary ammonium compound is benzalkonium chloride.

22. (Previously presented) The aqueous liquid preparation according to claim 1, which further includes one or more additives selected from the group consisting of a preservative, buffer, thickener, stabilizer, chelating agent, and pH controlling agent.

23. (Previously presented) The aqueous liquid preparation according to claim 22, wherein said preservative is benzalkonium chloride; wherein said buffer is boric acid and/or sodium borate; wherein said thickener is polyvinylpyrrolidone; wherein said stabilizer is sodium sulfite; wherein said chelating agent is sodium edetate; and wherein said pH controlling agent is sodium hydroxide.

24. (Previously presented) The aqueous liquid preparation according to claim 1, wherein the concentration of the 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt is about 0.2 w/v %.

25. (Previously presented) The aqueous liquid preparation according to claim 1, wherein the hydrate is at least one selected from a 1/2 hydrate, 1 hydrate and 3/2 hydrate.

26-28. (Canceled)

REMARKS

Favorable reconsideration is respectfully requested in view of the foregoing amendments and following remarks.

I. Examiner Interview

The Applicants express their sincere appreciation to the Examiner for her suggested claim amendments.

The claims have been amended as suggested by the Examiner. Applicant appreciates the Examiner's offer to enter these amendments after final.

II. Grounds of Rejection

All grounds of rejection are believed to be overcome as applied to the amended claims based upon the interview with the Examiner.

III. Conclusion

In view of the foregoing, it is believed that each ground of rejection set forth in the Official Action has been overcome, and that the application is now in condition for allowance.

Accordingly, such allowance is solicited.

Respectfully submitted,

/Warren M. Cheek, Jr./

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Date: 2013.05.20 14:12:07 -04'00'

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May 20, 2013

Electronic Acknowledgement Receipt

EFS ID:	15818273
Application Number:	13353653
International Application Number:	
Confirmation Number:	1077
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./ann leveille
Filer Authorized By:	Warren M. Cheek Jr.
Attorney Docket Number:	2012_0088
Receipt Date:	20-MAY-2013
Filing Date:	19-JAN-2012
Time Stamp:	15:28:01
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		AttachA_Amdt.pdf	190747 683abbc49bafd3bf81c8f8ff97a32f1d948f409f	yes	5

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Amendment After Final	1	1
	Claims	2	4
	Applicant Arguments/Remarks Made in an Amendment	5	5

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Information:

Total Files Size (in bytes):	190747

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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.

PTO/SB/06 (09-11)
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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 13/353,653	Filing Date 01/19/2012	☐ To be Mailed

ENTITY: ☒ LARGE ☐ SMALL ☐ MICRO

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).			
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))				
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT **05/20/2013**

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	* 17	Minus	** 25	= 0	X $80 =	0
Independent (37 CFR 1.16(h))	* 4	Minus	***4	= 0	X $420 =	0
☐ Application Size Fee (37 CFR 1.16(s))						
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
					TOTAL ADD'L FEE	0

AMENDMENT

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =	
Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =	
☐ Application Size Fee (37 CFR 1.16(s))						
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
					TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

LIE
/PAUL STANBACK/

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/353,653	01/19/2012	Shirou Sawa	2012_0088	1077

513 7590 05/10/2013

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	

NOTIFICATION DATE	DELIVERY MODE
05/10/2013	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

ddalecki@wenderoth.com
eoa@wenderoth.com

Office Action Summary	Application No. 13/353,653	Applicant(s) SAWA ET AL.	
	Examiner LAYLA SOROUSH	Art Unit 1627	AIA (First Inventor to File) Status No

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

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 January 2013*.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ 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.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

5)☒ Claim(s) *1,4,5,8,9,11-14,16-25 and 28* is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *1,4,5,8,9,11-14,16-25 and 28* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

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. _____.

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)).

* See the attached detailed Office action for a list of the certified copies not received.

Interim copies:

a)☐ All b)☐ Some c)☐ None of the: Interim copies of the priority documents have been received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)

2) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

4) ☐ Other: _____.

DETAILED ACTION

The Office Action is in response to the Applicant's reply filed January 30, 2013 and to the Office action mailed on August 30, 2012.

Response to Arguments

Applicant's arguments over the 35 U.S.C. 112 second rejection is persuasive in view of amendments made to the claims.

Applicant's arguments are directed to the Rule 1.132 Declaration filed January 30, 2013. Experiments 1 to 3 (results seen in the Tables) of the declaration were executed by Mr. Shirou Sawa. Specifically, in 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. As is apparent from Table 3, the preservative effect of the composition containing 0.02 w/v % of polyoxyl 40 stearate was found to be compatible with EP-criteria B in the European Pharmacopoeia (EP) (The EP-criteria B are described on p. 10 of Applicants response filed January 30, 2013). Applicant's 132 Declaration has been considered but is not persuasive. The Declaration does not commensurate in scope with the claimed limitations. More

specifically, the claims are drawn to 2-amino-3- (4-bromobenzoyl)phenylacetate in general in combination with any polyetheylene glycol fatty acid ester. Therefore, the rejections are modified below in view of the amendments.

The arguments are not persuasive and the rejection is made **FINAL**.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claim 1, 4-5, 8, 19-20, 22, and 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chen et al. (US 6383471), as applied to claims above, and further in view of Fukahori et al. (JP 402083323A).

Chen et al. teaches 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).

Although, the reference teaches both 2-amino-3-(4-bromobenzoyl)phenalyacetic acid and a polyethylene glycol fatty acid monoester dispersed with water, the reference fails to specify an example. Further, Chen et al. fails to teach the specified amount of surfactant.

Fukahori et al. teaches a stable aqueous solution of riboflavin containing non-ionic surfactants preferably polyoxyethylene hardened castor oil or polyethylene glycol monostearate in an amount of 0.01 to 5.0 wt %/vol%.

It would have been obvious to one of ordinary skill in the art to use a hydrophobic therapeutic agent, bromfenac, with a surfactant. The motivation comes from the teaching of Chen et al. that a variety of PEG-fatty acid esters have useful surfactant properties. Among the PEG-fatty acid monoesters, esters of lauric acid, oleic acid, and stearic acid are most useful. Hence, a skilled artisan would have reasonable expectation of successfully producing a composition with the most useful surfactant properties. Additionally, in the absence of showing the criticality, the determination of optimal or workable concentration of the polyethylene glycol monostearate by routine experimentation is obvious absent showing of criticality of the claimed concentration. One having ordinary skill in the art would have been motivated to do this to obtain the desired stability and solubilizing properties of the composition. Hence, a skilled artisan would have had reasonable expectation of successfully producing a composition with the polyethylene glycol monostearate in the claimed range.

With respect to claim 19, the transitional phrase “consisting essentially of” limits the scope of a claim to the specified materials or steps “and those that do not materially affect the basic and novel characteristic(s)” of the claimed invention. In re Herz, 537 F.2d 549, 551-52, 190 USPQ 461, 463 (CCPA 1976). “A consisting essentially of' claim occupies a middle ground between closed claims that are written in a consisting of' format and fully open claims that are drafted in a comprising' format.” PPG Industries v.

Guardian Industries, 156 F.3d 1351, 1354, 48 USPQ2d 1351, 1353-54 (Fed. Cir. 1998). See also Atlas Powder v. E.I. duPont de Nemours & Co., 750 F.2d 1569, 224 USPQ 409 (Fed. Cir. 1984); In re Janakirama-Rao, 317 F.2d 951, 137 USPQ 893 (CCPA 1963); Water Technologies Corp. vs. Calco, Ltd., 850 F.2d 660, 7 USPQ2d 1097 (Fed. Cir. 1988). For art purposes, "the consisting essentially of" language in the claim is treated as "comprising" language and it is an applicant's burden to establish that a step practiced in a prior art method is excluded from his claims by consisting essentially of' language." (See MPEP 2111.03)

Claims 1, 4-5, 9, 11-14, 19-22, and 28 are rejected under 35 U.S.C. 103(a) as being unpatentable Sawa (5942508) in view of Chen et al. (US 6383471), and further in view of Fukahori et al. (JP 402083323A).

Sawa teaches an aqueous solution comprising a pyridonecarboxylic acid selected from the group consisting of lomefloxacin, norfloxacin, enoxacin, ofloxacin, ciprofloxacin, tosufloxacin, fleroxacin, cinoxacin, levofloxacin and sparfloxacin or a pharmacologically acceptable salt thereof in a concentration of 0.2-5.0 (w/v)%, and an arylcarboxylic acid selected from the group consisting of pranoprofen, ibuprofen, bromfenac (2-amino-3-(4-bromobenzoyl)phenalyacetic acid), 2-naphthoic acid, 2-naphthylacetic acid and 2-naphthoxyacetic acid or a pharmacologically acceptable salt thereof in a proportion of 0.001-50 parts by weight per part by weight of the pyridonecarboxylic acid (see claim 2). The reference further teaches examples of the solubilizer include non-ionic surfactants such as polyoxyethylenesorbitane monoolate,

polyoxyethyleneoxystearic acid triglyceride, polyethylene glycol, polyoxyethylene hydrogenated castor oil and the like, (col 8 lines 66-67 and col 9 lines 1-3). The aqueous solution of the present invention is used as an eye drop, nasal drop or ear drop. When it is used as an eye drop, its pH is generally adjusted to about 3.5-8.5, preferably about 6-8, when it is used as a nasal drop, its pH is generally adjusted to about 3.5-8.5, preferably about 6-8, (See claims 3-5). Examples of the antiseptic include quaternary ammonium salts such as benzalkonium chloride. Examples of the thickener include polyvinylpyrrolidone, Examples of the chelating agent include sodium edetate, pH adjusting agents include sodium hydroxide, the reference teaches boric acid.

Although, the reference teaches both 2-amino-3-(4-bromobenzoyl)phenalyacetic acid and a surfactant in an aqueous solution, the reference fails to specify an example and the specific elected species of the surfactant. Sawa and Chen et al. fail to teach the specified amount of surfactant.

Chen et al. teaches 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. Chen et al. further teaches components that can be incorporated into the composition include inorganic acids inclusive of boric acid, solubilizer such as polyvinylpyrrolidone, exemplifications of carriers comprising Edetate Disodium, and ionizing agents that

deprotonate the acidic functional groups of the therapeutic agent are pharmaceutically acceptable organic or inorganic bases, inclusive of sodium hydroxide (reads on the limitations of claim 22).

Fukahori et al. teaches a stable aqueous solution of riboflavin containing non-ionic surfactants preferably polyoxyethylene hardened castor oil or polyethylene glycol monostearate in an amount of 0.01 to 5.0 wt %/vol%.

It would have been obvious to one of ordinary skill in the art to use a hydrophobic therapeutic agent, bromfenac, with the elected surfactant. The motivation comes from the teaching of Chen et al. that a variety of PEG-fatty acid esters have useful surfactant properties. Among the PEG-fatty acid monoesters, esters of lauric acid, oleic acid, and stearic acid are most useful. Hence, a skilled artisan would have reasonable expectation of successfully producing a composition with the most useful surfactant properties. Additionally, in the absence of showing the criticality, the determination of optimal or workable concentration of the polyethylene glycol monostearate within the reference's generic disclosure by routine experimentation is obvious absent showing of criticality of the claimed concentration. One having ordinary skill in the art would have been motivated to do this to obtain the desired clarity of the composition. Hence, a skilled artisan would have had reasonable expectation of successfully producing a composition with the polyethylene glycol monostearate in the claimed range.

With respect to claim 19, the transitional phrase “consisting essentially of” limits the scope of a claim to the specified materials or steps “and those that do not materially affect the basic and novel characteristic(s)” of the claimed invention. In re Herz, 537 F.2d 549, 551-52, 190 USPQ 461, 463 (CCPA 1976). “A consisting essentially of' claim occupies a middle ground between closed claims that are written in a consisting of' format and fully open claims that are drafted in a comprising' format.” PPG Industries v. Guardian Industries, 156 F.3d 1351, 1354, 48 USPQ2d 1351, 1353-54 (Fed. Cir. 1998). See also Atlas Powder v. E.I. duPont de Nemours & Co., 750 F.2d 1569, 224 USPQ 409 (Fed. Cir. 1984); In re Janakirama-Rao, 317 F.2d 951, 137 USPQ 893 (CCPA 1963); Water Technologies Corp. vs. Calco, Ltd., 850 F.2d 660, 7 USPQ2d 1097 (Fed. Cir. 1988). For art purposes, “the consisting essentially of” language in the claim is treated as “comprising” language and it is an applicant's burden to establish that a step practiced in a prior art method is excluded from his claims by consisting essentially of' language.” (See MPEP 2111.03)

Claim 1, 4-5, 8-9, 11-14, 19-22, and 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sawa (6274592) in view of Chen et al. (US 6383471), as applied to claims and further in view of Fukahori et al. (JP 402083323A).

Sawa teaches an aqueous solution containing an arylcarboxylic acid or a pharmacologically acceptable salt thereof, particularly pranoprofen, dicrofenac or bromfenac(2-amino-3-(4-bromobenzoyl)phenalyacetic acid), and which has sufficient stability at lower temperatures. Examples of the solubilizer include non-ionic surfactants

such as polyoxyethylenesorbitan monoolate, polyoxyethyleneoxystearic acid triglyceride, polyethylene glycol, polyoxyethylene hydrogenated castor oil and the like, (see col 11 lines 59-63). The aqueous solution of the present invention is used as an eye drop, nasal drop or ear drop. When it is used as an eye drop, its pH is generally adjusted to about 3.5-8.5, preferably about 6-8, when it is used as a nasal drop, its pH is generally adjusted to about 3.5-8.5, preferably about 6-8. Examples of the antiseptic include quaternary ammonium salts such as benzalkonium chloride. Examples of the thickener include polyvinylpyrrolidone, Examples of the chelating agent include sodium edetate, pH adjusting agents include sodium hydroxide, the reference teaches boric acid.

Although, the reference teaches both 2-amino-3-(4-bromobenzoyl)phenalyacetic acid and a surfactant in an aqueous solution, the reference fails to specify an example and the specific elected species of the surfactant. Sawa and Chen et al. fail to teach the specified amount of surfactant.

Chen et al. teaches 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. Chen et al. further teaches components that can be incorporated into the composition include inorganic acids inclusive of boric acid, solubilizer such as polyvinylpyrrolidone, exemplifications of carriers comprising Edetate Disodium, and ionizing agents that

deprotonate the acidic functional groups of the therapeutic agent are pharmaceutically acceptable organic or inorganic bases, inclusive of sodium hydroxide (reads on the limitations of claim 22).

Fukahori et al. teaches a stable aqueous solution of riboflavin containing non-ionic surfactants preferably polyoxyethylene hardened castor oil or polyethylene glycol monostearate in an amount of 0.01 to 5.0 wt %/vol%.

It would have been obvious to one of ordinary skill in the art to use a hydrophobic therapeutic agent, bromfenac, with the elected surfactant. The motivation comes from the teaching of Chen et al. that a variety of PEG-fatty acid esters have useful surfactant properties. Among the PEG-fatty acid monoesters, esters of lauric acid, oleic acid, and stearic acid are most useful. Hence, a skilled artisan would have reasonable expectation of successfully producing a composition with the most useful surfactant properties. Additionally, in the absence of showing the criticality, the determination of optimal or workable concentration of the polyethylene glycol monostearate within the reference's generic disclosure by routine experimentation is obvious absent showing of criticality of the claimed concentration. One having ordinary skill in the art would have been motivated to do this to obtain the desired clarity of the composition. Hence, a skilled artisan would have had reasonable expectation of successfully producing a composition with the polyethylene glycol monostearate in the claimed range.

With respect to claim 19, the transitional phrase “consisting essentially of” limits the scope of a claim to the specified materials or steps “and those that do not materially affect the basic and novel characteristic(s)” of the claimed invention. In re Herz, 537 F.2d 549, 551-52, 190 USPQ 461, 463 (CCPA 1976). “A consisting essentially of' claim occupies a middle ground between closed claims that are written in a consisting of' format and fully open claims that are drafted in a comprising' format.” PPG Industries v. Guardian Industries, 156 F.3d 1351, 1354, 48 USPQ2d 1351, 1353-54 (Fed. Cir. 1998). See also Atlas Powder v. E.I. duPont de Nemours & Co., 750 F.2d 1569, 224 USPQ 409 (Fed. Cir. 1984); In re Janakirama-Rao, 317 F.2d 951, 137 USPQ 893 (CCPA 1963); Water Technologies Corp. vs. Calco, Ltd., 850 F.2d 660, 7 USPQ2d 1097 (Fed. Cir. 1988). For art purposes, “the consisting essentially of” language in the claim is treated as “comprising” language and it is an applicant's burden to establish that a step practiced in a prior art method is excluded from his claims by consisting essentially of' language.” (See MPEP 2111.03)

Claim 1, 4-5, 8, 13, 19-20, 22, and 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sawa (20010056098) in view of Chen et al. (US 6383471), as applied to claims further in view of Fukahori et al. (JP 402083323A).

Sawa teaches an aqueous solution which contains an arylcarboxylic acid or a pharmacologically acceptable salt thereof, particularly pranoprofen, dicrofenac or bromfenac (2-amino-3-(4-bromobenzoyl)phenalyacetic acid), and which has sufficient

stability at lower temperatures[0004]. Examples of the solubilizer include non-ionic surfactants such as polyoxyethylenesorbitan monoolate, polyoxyethyleneoxystearic acid triglyceride, polyethylene glycol, polyoxyethylene hydrogenated castor oil and the like, [0147]. The aqueous solution of the present invention is used as an eye drop, nasal drop or ear drop. When it is used as an eye drop, its pH is generally adjusted to about 3.5-8.5, preferably about 6-8, when it is used as a nasal drop, its pH is generally adjusted to about 3.5-8.5, preferably about 6-8. Examples of the antiseptic include quaternary ammonium salts such as benzalkonium chloride. Examples of the thickener include polyvinylpyrrolidone, Examples of the chelating agent include sodium edetate, pH adjusting agents include sodium hydroxide, the reference teaches boric acid.

Although, the reference teaches both 2-amino-3-(4-bromobenzoyl)phenalyacetic acid and a surfactant in an aqueous solution, the reference fails to specify an example and the specific elected species of the surfactant. Sawa and Chen et al. fail to teach the specified amount of surfactant.

Chen et al. teaches 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. Chen et al. further teaches components that can be incorporated into the composition include inorganic acids inclusive of boric acid, solubilizer such as polyvinylpyrrolidone,

exemplifications of carriers comprising Edetate Disodium, and ionizing agents that deprotonate the acidic functional groups of the therapeutic agent are pharmaceutically acceptable organic or inorganic bases, inclusive of sodium hydroxide (reads on the limitations of claim 22).

Fukahori et al. teaches a stable aqueous solution of riboflavin containing non-ionic surfactants preferably polyoxyethylene hardened castor oil or polyethylene glycol monostearate in an amount of 0.01 to 5.0 wt %/vol%.

It would have been obvious to one of ordinary skill in the art to use a hydrophobic therapeutic agent, bromfenac, with the elected surfactant. The motivation comes from the teaching of Chen et al. that a variety of PEG-fatty acid esters have useful surfactant properties. Among the PEG-fatty acid monoesters, esters of lauric acid, oleic acid, and stearic acid are most useful. Hence, a skilled artisan would have reasonable expectation of successfully producing a composition with the most useful surfactant properties. Additionally, in the absence of showing the criticality, the determination of optimal or workable concentration of the polyethylene glycol monostearate within the reference's generic disclosure by routine experimentation is obvious absent showing of criticality of the claimed concentration. One having ordinary skill in the art would have been motivated to do this to obtain the desired clarity of the composition. Hence, a skilled artisan would have had reasonable expectation of successfully producing a composition with the polyethylene glycol monostearate in the claimed range.

With respect to claim 19, the transitional phrase “consisting essentially of” limits the scope of a claim to the specified materials or steps “and those that do not materially affect the basic and novel characteristic(s)” of the claimed invention. In re Herz, 537 F.2d 549, 551-52, 190 USPQ 461, 463 (CCPA 1976). “A consisting essentially of' claim occupies a middle ground between closed claims that are written in a consisting of' format and fully open claims that are drafted in a comprising' format.” PPG Industries v. Guardian Industries, 156 F.3d 1351, 1354, 48 USPQ2d 1351, 1353-54 (Fed. Cir. 1998). See also Atlas Powder v. E.I. duPont de Nemours & Co., 750 F.2d 1569, 224 USPQ 409 (Fed. Cir. 1984); In re Janakirama-Rao, 317 F.2d 951, 137 USPQ 893 (CCPA 1963); Water Technologies Corp. vs. Calco, Ltd., 850 F.2d 660, 7 USPQ2d 1097 (Fed. Cir. 1988). For art purposes, “the consisting essentially of” language in the claim is treated as “comprising” language and it is an applicant's burden to establish that a step practiced in a prior art method is excluded from his claims by consisting essentially of' language.” (See MPEP 2111.03)

Claims 9, 11- 14, and 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chen et al. (US 6383471) and Fukahori et al. (JP 402083323A), as applied to claims 1, 4-5, 8, 19-20, 22, and 28 above, and further in view of Sawa (5942508).

Chen et al. is as discussed above.

Chen et al. fails to teach the pH range claimed, or that the ocular preparation is an eye drop, a nasal drop, and the preservative being a quaternary ammonium compound - benzalkonium chloride.

Sawa teaches an aqueous solution comprising a pyridonecarboxylic acid selected from the group consisting of lomefloxacin, norfloxacin, enoxacin, ofloxacin, ciprofloxacin, tosufloxacin, fleroxacin, cinoxacin, levofloxacin and sparfloxacin or a pharmacologically acceptable salt thereof in a concentration of 0.2-5.0 (w/v)%, and an arylcarboxylic acid selected from the group consisting of pranoprofen, ibuprofen, bromfenac, 2-naphthoic acid, 2-naphthylacetic acid and 2-naphthoxyacetic acid or a pharmacologically acceptable salt thereof in a proportion of 0.001-50 parts by weight per part by weight of the pyridonecarboxylic acid (see claim 2). The reference further teaches examples of the solubilizer include non-ionic surfactants such as polyoxyethylenesorbitane monoolate, polyoxyethyleneoxystearic acid triglyceride, polyethylene glycol, polyoxyethylene hydrogenated castor oil and the like, (col 8 lines 66-67 and col 9 lines 1-3). The aqueous solution of the present invention is used as an eye drop, nasal drop or ear drop. When it is used as an eye drop, its pH is generally adjusted to about 3.5-8.5, preferably about 6-8, when it is used as a nasal drop, its pH is generally adjusted to about 3.5-8.5, preferably about 6-8, (See claims 3-5). Examples of the antiseptic include quaternary ammonium salts such as benzalkonium chloride. Examples of the thickener include polyvinylpyrrolidone, Examples of the chelating agent include sodium edetate, pH adjusting agents include sodium hydroxide, the reference teaches boric acid.

It would have been obvious to one of ordinary skill in the art to use a preservative or specifically - benzalkonium chloride, making the pH range claimed, and an eye and nasal drop. The motivation comes from the teaching of Sawa that a an aqueous solution comprising bromfenac and non-ionic surfactants comprise benzalkonium chloride for its antiseptic properties; the formlation are present as eye drop, nasal drop or ear drop. When it is used as an eye drop, its pH is generally adjusted to about 3.5-8.5, preferably about 6-8, when it is used as a nasal drop, its pH is generally adjusted to about 3.5-8.5, preferably about 6-8. Hence, a skilled artisan would have reasonable expectation of successfully producing a composition with similar efficacy and results.

Claims 9, 11-14, and 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chen et al. (US 6383471) and Fukahori et al. (JP 402083323A), as applied to 1, 4-5, 8, 19-20, 22, and 28 above, and further in view of Sawa (6274592).

Chen et al. is as discussed above.

Chen et al. fails to teach the pH range claimed, or that the ocular preparation is an eye drop an eye drop, a nasal drop, and the perservative being a quaternary ammonium compound - benzalkonium chloride.

Sawa teaches an aqueous solution containing an arylcarboxylic acid or a pharmacologically acceptable salt thereof, particularly pranoprofen, dicrofenac or bromfenac, and which has sufficient stability at lower temperatures. Examples of the solubilizer include non-ionic surfactants such as polyoxyethylenesorbitan monoolate, polyoxyethyleneoxystearic acid triglyceride, polyethylene glycol, polyoxyethylene

hydrogenated castor oil and the like, (see col 11 lines 59-63). The aqueous solution of the present invention is used as an eye drop, nasal drop or ear drop. When it is used as an eye drop, its pH is generally adjusted to about 3.5-8.5, preferably about 6-8, when it is used as a nasal drop, its pH is generally adjusted to about 3.5-8.5, preferably about 6-8. Examples of the antiseptic include quaternary ammonium salts such as benzalkonium chloride. Examples of the thickener include polyvinylpyrrolidone, Examples of the chelating agent include sodium edetate, pH adjusting agents include sodium hydroxide, the reference teaches boric acid.

It would have been obvious to one of ordinary skill in the art to use a preservative or specifically - benzalkonium chloride, making the pH range claimed, and a nasal drop. The motivation comes from the teaching of Sawa that a an aqueous solution comprising bromfenac and non-ionic surfactants comprise benzalkonium chloride for its antiseptic properties; the formlation are present as eye drop, nasal drop or ear drop. When it is used as an eye drop, its pH is generally adjusted to about 3.5-8.5, preferably about 6-8, when it is used as a nasal drop, its pH is generally adjusted to about 3.5-8.5, preferably about 6-8. Hence, a skilled artisan would have reasonable expectation of successfully producing a composition with similar efficacy and results.

Claims 9, 11- 14, and 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chen et al. (US 6383471) and Fukahori et al. (JP 402083323A), as applied to claims 1, 4-5, 8, 19-20, 22, and 28 above, and further in view of Sawa (20010056098).

Chen et al. is as discussed above.

Chen et al. fails to teach the pH range claimed, or that the ocular preparation is an eye drop, a nasal drop, and the perservative being a quaternary ammonium compound - benzalkonium chloride.

Sawa teaches an aqueous solution which contains an arylcarboxylic acid or a pharmacologically acceptable salt thereof, particularly pranoprofen, dicrofenac or bromfenac, and which has sufficient stability at lower temperatures[0004]. Examples of the solubilizer include non-ionic surfactants such as polyoxyethylenesorbitan monoolate, polyoxyethyleneoxystearic acid triglyceride, polyethylene glycol, polyoxyethylene hydrogenated castor oil and the like, [0147]. The aqueous solution of the present invention is used as an eye drop, nasal drop or ear drop. When it is used as an eye drop, its pH is generally adjusted to about 3.5-8.5, preferably about 6-8, when it is used as a nasal drop, its pH is generally adjusted to about 3.5-8.5, preferably about 6-8. Examples of the antiseptic include quaternary ammonium salts such as benzalkonium chloride. Examples of the thickener include polyvinylpyrrolidone, Examples of the chelating agent include sodium edetate, pH adjusting agents include sodium hydroxide, the reference teaches boric acid.

It would have been obvious to one of ordinary skill in the art to use a preservative or specifically - benzalkonium chloride, making the pH range claimed, and a nasal drop. The motivation comes from the teaching of Sawa that a an aqueous solution comprising bromfenac and non-ionic surfactants comprise benzalkonium chloride for its antiseptic

properties; the formulation are present as eye drop, nasal drop or ear drop. When it is used as an eye drop, its pH is generally adjusted to about 3.5-8.5, preferably about 6-8, when it is used as a nasal drop, its pH is generally adjusted to about 3.5-8.5, preferably about 6-8. Hence, a skilled artisan would have reasonable expectation of successfully producing a composition with similar efficacy and results.

Claims 9, 21, and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chen et al. (US 6383471) and Fukahori et al. (JP 402083323A), as applied to claims 1, 4-5, 8, 19-20, 22, and 28 above, and further in view of Gamache et al. (WO 01/15677) and Yakuji Nippo Ltd., ("New Drugs in Japan: 2001", 2001 Edition, Published by May 11, 2001, p.27-29 - IDS).

Chen et al. is as discussed above.

Chen et al. fails to teach the specified preservative and stabilizer.

Gamache et al. teaches anti-inflammatory agents include bromfenac and Moxifloxacin, viscosity building agents include, for example, polyvinyl alcohol, polyvinyl pyrrolidone, methyl cellulose, hydroxypropyl methylcellulose, hydroxyethyl cellulose, carboxymethyl cellulose, hydroxypropyl cellulose or other agents known to those skilled in the art. An appropriate buffer system (e. g., sodium phosphate, sodium acetate or sodium borate) may be added to prevent pH drift under storage conditions. Exemplified is an otic/nasal suspension: Ingredient 1B/1 D agonist 0.1-1.0% w/v, Moxifloxacin 0.3% w/v, Benzalkonium Chloride 0.01% w/v, Edetate Disodium, USP 0.01% w/v, Sodium

Chloride, USP 0.3% w/v, Sodium Sulfate, USP 1.2% w/v, Tyloxapol, USP 0.05% w/v, Hydroxyethylcellulose 0.25% w/v, Sulfuric Acid and/or Sodium Hydroxide, NF q. s., and purified water q. s. to 100%.

Yakuji Nippo Ltd. teaches an aqueous ophthalmic solution comprising bromfenac sodium hydrate boric acid, sodium sulfite, disodium edetate, polyvinylpyrroldione, benzalkonium sodium hydrate.

It would have been obvious to one of ordinary skill in the art at the time of the invention to use the specific preservative Benzalkonium Chloride and stabilizer - sodium sulfite. The motivation comes from the teaching of Gamache et al. that the preservatives inclusive of Benzalkonium Chloride prevent microbial contamination during use and the stabilizer prevent pH drift under storage conditions and further by Yakuji Nippo Ltd. that an ophthalmic solution of bromfenac sodium hydrate comprises boric acid, sodium sulfite, disodium edetate, polyvinylpyrroldione, benzalkonium sodium hydrate. Hence, a skilled artisan would have had reasonable expectation of successfully producing a composition with similar efficacy and results.

Claims 10, and 23-25 are rejected under 35 U.S.C. 103(a) as being unpatentable Sawa (5942508) in view of Chen et al. (US 6383471) and Fukahori et al. (JP 402083323A), as applied to claims 1, 4-5, 9, 11-14, 19-22, and 28 above, and further in view of Gamache et al. (WO 01/15677) and Yakuji Nippo Ltd., ("New Drugs in Japan: 2001", 2001 Edition, Published by May 11, 2001, p.27-29 - IDS).

Sawa and Chen et al. is as discussed above.

Sawa and Chen et al. fail to teach the specified sodium sulfite and the specified sodium salt or a hydrate.

Gamache et al. teaches anti-inflammatory agents include bromfenac and Moxifloxacin, viscosity building agents include, for example, polyvinyl alcohol, polyvinyl pyrrolidone, methyl cellulose, hydroxypropyl methylcellulose, hydroxyethyl cellulose, carboxymethyl cellulose, hydroxypropyl cellulose or other agents known to those skilled in the art. An appropriate buffer system (e. g., sodium phosphate, sodium acetate or sodium borate) may be added to prevent pH drift under storage conditions. Exemplified is an otic/nasal suspension: Ingredient 1B/1 D agonist 0.1-1.0% w/v, Moxifloxacin 0.3% w/v, Benzalkonium Chloride 0.01% w/v, Edetate Disodium, USP 0.01% w/v, Sodium Chloride, USP 0.3% w/v, Sodium Sulfate, USP 1.2% w/v, Tyloxapol, USP 0.05% w/v, Hydroxyethylcellulose 0.25% w/v, Sulfuric Acid and/or Sodium Hydroxide, NF q. s., and purified water q. s. to 100%.

Yakuji Nippo Ltd. teaches an aqueous ophthalmic solution comprising bromfenac sodium hydrate boric acid, sodium sulfite, disodium edetate, polyvinylpyrroldione, benzalkonium sodium hydrate.

It would have been obvious to one of ordinary skill in the art at the time of the invention to use the specific stabilizer - sodium sulfite. The motivation comes from the teaching of Gamache et al. that the stabilizer prevents pH drift under storage conditions and further by Yakuji Nippo Ltd. that an ophthalmic solution of bromfenac sodium hydrate comprises boric acid, sodium sulfite, disodium edetate, polyvinylpyrroldione,

benzalkonium sodium hydrate. Hence, a skilled artisan would have had reasonable expectation of successfully producing a composition with similar efficacy and results.

Claims 10, and 23-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sawa (6274592) in view of Chen et al. (US 6383471) and Fukahori et al. (JP 402083323A), as applied to claims 1, 4-5, 8-9, 11-14, 19-22, and 28 above, and further in view of Gamache et al. (WO 01/15677) and Yakuji Nippo Ltd., ("New Drugs in Japan: 2001", 2001 Edition, Published by May 11, 2001, p.27-29 - IDS).

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Yakuji Nippo Ltd. teaches an aqueous ophthalmic solution comprising bromfenac sodium hydrate boric acid, sodium sulfite, disodium edetate, polyvinylpyrroldione, benzalkonium sodium hydrate.

It would have been obvious to one of ordinary skill in the art at the time of the invention to use the specific stabilizer - sodium sulfite. The motivation comes from the teaching of Gamache et al. that the stabilizer prevents pH drift under storage conditions and further by Yakuji Nippo Ltd. that an ophthalmic solution of bromfenac sodium hydrate comprises boric acid, sodium sulfite, disodium edetate, polyvinylpyrroldione, benzalkonium sodium hydrate. Hence, a skilled artisan would have had reasonable expectation of successfully producing a composition with similar efficacy and results.

Claims 10, and 23-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sawa (20010056098) in view of Chen et al. (US 6383471) and Fukahori et al. (JP 402083323A), as applied to claims 1, 4-5, 8, 13, 19-20, 22, and 28 above, and further in view of Gamache et al. (WO 01/15677) and Yakuji Nippo Ltd., ("New Drugs in Japan: 2001", 2001 Edition, Published by May 11, 2001, p.27-29 - IDS).

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Claim 16 is rejected under 35 U.S.C. 103(a) as being unpatentable over Chen et al. (US 6383471) and Fukahori et al. (JP 402083323A), as applied to claims 1, 4-5, 8, 19-20, 22, and 28 above, and further in view of Aikawa et al. (JP 2002308764 A).

Chen et al. and Fukahori et al. are as discussed above.

Chen et al. and Fukahori et al. fail to teach the specified sodium salt or a hydrate.

Aikawa et al. teaches ophthalmic pharmaceutical composition (eye drop) for treating or preventing congestion symptom of a conjunctiva, contains bromfenac sodium hydrate.

It would have been obvious to one of ordinary skill in the art to use the sodium salt and hydrate of bromfenac. The motivation comes from the teaching of Aikawa et al. that an aqueous solution (eye drop) comprising bromfenac sodium hydrate treats or prevents congestion symptom of a conjunctiva. Hence, a skilled artisan would have reasonable expectation of successfully producing a composition with similar efficacy and results.

Claim 16 is rejected under 35 U.S.C. 103(a) as being unpatentable Sawa (5942508) in view of Chen et al. (US 6383471) and Fukahori et al. (JP 402083323A), as applied to claims 1, 4-5, 9, 11-14, 19-22, and 28 above, and further in view of Aikawa et al. (JP 2002308764 A).

Sawa, Chen et al. and Fukahori et al. are as discussed above.

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Claim 16 is rejected under 35 U.S.C. 103(a) as being unpatentable over Sawa (20010056098) in view of Chen et al. (US 6383471) and Fukahori et al. (JP 402083323A), as applied to claims 1, 4-5, 8, 13, 19-20, 22, and 28 above, and further in view of Aikawa et al. (JP 2002308764 A).

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Aikawa et al. teaches ophthalmic pharmaceutical composition (eye drop) for treating or preventing congestion symptom of a conjunctiva, contains bromfenac sodium hydrate.

It would have been obvious to one of ordinary skill in the art to use the sodium salt and hydrate of bromfenac. The motivation comes from the teaching of Aikawa et al. that an aqueous solution (eye drop) comprising bromfenac sodium hydrate treats or prevents congestion symptom of a conjunctiva. Hence, a skilled artisan would have

reasonable expectation of successfully producing a composition with similar efficacy and results.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 4-5, 8, 11-14, 19-20, 22, and 27 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-3 and 5-6 of U.S. Patent No. 7829544 in view of Chen et al. (US 6383471). Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims are drawn to an aqueous solution preparation according to claim 1, wherein the concentration of the aminoglycoside antibiotic or its pharmacologically acceptable salt in the aqueous solution preparation is within a range from a minimum of 0.01 w/v % to a maximum of 35.0 w/v %, and the concentration of the bromfenac or its pharmacologically acceptable salt in the aqueous solution preparation is within a range from a minimum of 0.01 w/v % to a maximum of 0.5 w/v %; further comprising at least one compound selected from the group consisting of a nonionic water-soluble polymer and a nonionic surfactant whereas the claims herein are drawn to an aqueous liquid preparation comprising 2-amino-3-(4- bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof, and an alkyl aryl polyether alcohol type polymer or a polyethylene glycol fatty acid ester.

Although, the reference teaches both 2-amino-3-(4-bromobenzoyl)phenalyacetic acid and a surfactant in an aqueous solution, the reference fails to specify an example and the specific elected species of the surfactant.

Chen et al. teaches 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. Chen et al. further teaches components that can be incorporated into the composition include inorganic acids inclusive of boric acid, solubilizer such as polyvinylpyrrolidone, exemplifications of carriers comprising Edetate Disodium, and ionizing agents that deprotonate the acidic functional groups of the therapeutic agent are pharmaceutically acceptable organic or inorganic bases, inclusive of sodium hydroxide (reads on the limitations of claim 22).

It would have been obvious to one of ordinary skill in the art to use a hydrophobic therapeutic agent, bromfenac, with the elected surfactant. The motivation comes from the teaching of Chen et al. that a variety of PEG-fatty acid esters have useful surfactant properties. Among the PEG-fatty acid monoesters, esters of lauric acid, oleic acid, and stearic acid are most useful. Hence, a skilled artisan would have reasonable expectation of successfully producing a composition with the most useful surfactant properties.

With respect to claim 19, the transitional phrase “consisting essentially of” limits the scope of a claim to the specified materials or steps “and those that do not materially affect the basic and novel characteristic(s)” of the claimed invention. In re Herz, 537 F.2d 549, 551-52, 190 USPQ 461, 463 (CCPA 1976). “A consisting essentially of' claim

occupies a middle ground between closed claims that are written in a consisting of' format and fully open claims that are drafted in a comprising' format." PPG Industries v. Guardian Industries, 156 F.3d 1351, 1354, 48 USPQ2d 1351, 1353-54 (Fed. Cir. 1998). See also Atlas Powder v. E.I. duPont de Nemours & Co., 750 F.2d 1569, 224 USPQ 409 (Fed. Cir. 1984); In re Janakirama-Rao, 317 F.2d 951, 137 USPQ 893 (CCPA 1963); Water Technologies Corp. vs. Calco, Ltd., 850 F.2d 660, 7 USPQ2d 1097 (Fed. Cir. 1988). For art purposes, "the consisting essentially of" language in the claim is treated as "comprising" language and it is an applicant's burden to establish that a step practiced in a prior art method is excluded from his claims by consisting essentially of' language." (See MPEP 2111.03)

Claim 7 is rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-3 and 5-6 of U.S. Patent No. 7829544 in view of Chen et al. (US 6383471), as applied to claims 1, 4-5, 8, 11-14, 19-20, 22, and 27 above and further in view of Fukahori et al. (JP 402083323A). Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims are drawn to an aqueous solution preparation according to claim 1, wherein the concentration of the aminoglycoside antibiotic or its pharmacologically acceptable salt in the aqueous solution preparation is within a range from a minimum of 0.01 w/v % to a maximum of 35.0 w/v %, and the concentration of the bromfenac or its pharmacologically acceptable salt in the aqueous solution preparation is within a range from a minimum of 0.01 w/v % to a maximum of 0.5 w/v %; further comprising at least one compound selected from the group consisting of a nonionic water-soluble polymer

and a nonionic surfactant whereas the claims herein are drawn to an aqueous liquid preparation comprising 2-amino-3-(4- bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof, and an alkyl aryl polyether alcohol type polymer or a polyethylene glycol fatty acid ester.

U.S. Patent No. 7829544 and Chen et al. (US 6383471) are discussed above.

U.S. Patent No. 7829544 and Chen et al. (US 6383471) fail to teach the amount of the polyethylene glycol as claimed.

Fukahori et al. teaches a stable aqueous solution of riboflavin containing non-ionic surfactants preferably polyoxyethylene hardened castor oil or polyethylene glycol monostearate in an amount of 0.01 to 5.0 wt %/vol%.

In the absence of showing the criticality, the determination of optimal or workable concentration of the polyethylene glycol monostearate by routine experimentation is obvious absent showing of criticality of the claimed concentration. One having ordinary skill in the art would have been motivated to do this to obtain the **desired stability and solubilizing** properties of the composition. Hence, a skilled artisan would have had reasonable expectation of successfully producing a composition with the polyethylene glycol monostearate in the claimed range.

Claims 9-10, 21, and 23-25 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-3 and 5-6 of

U.S. Patent No. 7829544 in view of Chen et al. (US 6383471), as applied to claims 1, 4-5, 8, 11-14, 19-20, 22, and 27 above and further in view of Gamache et al. (WO 01/15677) and Yakuji Nippo Ltd., ("New Drugs in Japan: 2001", 2001 Edition, Published by May 11, 2001, p.27-29 - IDS). Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims are drawn to an aqueous solution preparation according to claim 1, wherein the concentration of the aminoglycoside antibiotic or its pharmacologically acceptable salt in the aqueous solution preparation is within a range from a minimum of 0.01 w/v % to a maximum of 35.0 w/v %, and the concentration of the bromfenac or its pharmacologically acceptable salt in the aqueous solution preparation is within a range from a minimum of 0.01 w/v % to a maximum of 0.5 w/v %; further comprising at least one compound selected from the group consisting of a nonionic water-soluble polymer and a nonionic surfactant whereas the claims herein are drawn to an aqueous liquid preparation comprising 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof, and an alkyl aryl polyether alcohol type polymer or a polyethylene glycol fatty acid ester.

U.S. Patent No. 7829544 and Chen et al. (US 6383471) are discussed above.

U.S. Patent No. 7829544 and Chen et al. (US 6383471) fail to teach the specified preservative and stabilizer; or salt and hydrate.

Gamache et al. teaches anti-inflammatory agents include bromfenac and Moxifloxacin, viscosity building agents include, for example, polyvinyl alcohol, polyvinyl pyrrolidone, methyl cellulose, hydroxypropyl methylcellulose, hydroxyethyl cellulose,

carboxymethyl cellulose, hydroxypropyl cellulose or other agents known to those skilled in the art. An appropriate buffer system (e. g., sodium phosphate, sodium acetate or sodium borate) may be added to prevent pH drift under storage conditions. Exemplified is an otic/nasal suspension: Ingredient 1B/1 D agonist 0.1-1.0% w/v, Moxifloxacin 0.3% w/v, Benzalkonium Chloride 0.01% w/v, Edetate Disodium, USP 0.01% w/v, Sodium Chloride, USP 0.3% w/v, Sodium Sulfate, USP 1.2% w/v, Tyloxapol, USP 0.05% w/v, Hydroxyethylcellulose 0.25% w/v, Sulfuric Acid and/or Sodium Hydroxide, NF q. s., and purified water q. s. to 100%.

Yakuji Nippo Ltd. teaches an aqueous ophthalmic solution comprising bromfenac sodium hydrate boric acid, sodium sulfite, disodium edetate, polyvinylpyrroldione, benzalkonium sodium hydrate.

It would have been obvious to one of ordinary skill in the art at the time of the invention to use the specific preservative Benzalkonium Chloride and stabilizer - sodium sulfite. The motivation comes from the teaching of Gamache et al. that the preservatives inclusive of Benzalkonium Chloride prevent microbial contamination during use and the stabilizer prevent pH drift under storage conditions and further by Yakuji Nippo Ltd. that an ophthalmic solution of bromfenac sodium hydrate comprises boric acid, sodium sulfite, disodium edetate, polyvinylpyrroldione, benzalkonium sodium hydrate. Hence, a skilled artisan would have had reasonable expectation of successfully producing a composition with similar efficacy and results.

Claim 16 is rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-3 and 5-6 of U.S. Patent No. 7829544 in

view of Chen et al. (US 6383471) and Fukahori et al. (JP 402083323A), as applied to claims 1, 4-5, 7-8, 11-14, 19-20, 22, and 27 above and further in view of Aikawa et al. (JP 2002308764 A). Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims are drawn to an aqueous solution preparation according to claim 1, wherein the concentration of the aminoglycoside antibiotic or its pharmacologically acceptable salt in the aqueous solution preparation is within a range from a minimum of 0.01 w/v % to a maximum of 35.0 w/v %, and the concentration of the bromfenac or its pharmacologically acceptable salt in the aqueous solution preparation is within a range from a minimum of 0.01 w/v % to a maximum of 0.5 w/v %; further comprising at least one compound selected from the group consisting of a nonionic water-soluble polymer and a nonionic surfactant whereas the claims herein are drawn to an aqueous liquid preparation comprising 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof, and an alkyl aryl polyether alcohol type polymer or a polyethylene glycol fatty acid ester.

U.S. Patent No. 7829544 and Chen et al. (US 6383471) are discussed above.

U.S. Patent No. 7829544 and Chen et al. (US 6383471) fail to teach the amount of the polyethylene glycol as claimed.

Chen et al. and Fukahori et al. are as discussed above.

Chen et al. and Fukahori et al. fail to teach the specified sodium salt or a hydrate.

Aikawa et al. teaches ophthalmic pharmaceutical composition (eye drop) for treating or preventing congestion symptom of a conjunctiva, contains bromfenac sodium hydrate.

It would have been obvious to one of ordinary skill in the art to use the sodium salt and hydrate of bromfenac. The motivation comes from the teaching of Aikawa et al. that an aqueous solution (eye drop) comprising bromfenac sodium hydrate treats or prevents congestion symptom of a conjunctiva. Hence, a skilled artisan would have reasonable expectation of successfully producing a composition with similar efficacy and results.

Claims 1, 4-5, 8, 13-14, 19-20, 22, and 27 rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-5 of U.S. Patent No. 5942508 in view of Chen et al. (US 6383471). Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims are drawn to an aqueous solution comprising a pyridonecarboxylic acid selected from the group consisting of lomefloxacin, norfloxacin, enoxacin, ofloxacin, ciprofloxacin, tosufloxacin, fleroxacin, cinoxacin, levofloxacin and sparfloxacin or a pharmacologically acceptable salt thereof in a concentration of 0.2-5.0 (w/v)%, and an arylcarboxylic acid selected from the group consisting of pranoprofen, ibuprofen, bromfenac, 2-naphthoic acid, 2-naphthylacetic acid and 2-naphthoxyacetic acid or a pharmacologically acceptable salt thereof in a proportion of 0.001-50 parts by weight

per part by weight of the pyridonecarboxylic acid whereas the claims herein are drawn to an aqueous liquid preparation comprising 2-amino-3-(4- bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof, and an alkyl aryl polyether alcohol type polymer or a polyethylene glycol fatty acid ester.

Although, the reference teaches 2-amino-3-(4-bromobenzoyl)phenalyacetic acid in an eye and nasal drop the reference fails to specify an example and the specific elected species of the surfactant.

Chen et al. teaches 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). 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). 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

It would have been obvious to one of ordinary skill in the art to use a hydrophobic therapeutic agent, bromfenac, with the elected surfactant. The motivation comes from the teaching of Chen et al. that a variety of PEG-fatty acid esters have useful surfactant properties. Among the PEG-fatty acid monoesters, esters of lauric acid, oleic acid, and stearic acid are most useful. Hence, a skilled artisan would have reasonable expectation of successfully producing a composition with the most useful surfactant properties.

With respect to claim 19, the transitional phrase “consisting essentially of” limits the scope of a claim to the specified materials or steps “and those that do not materially affect the basic and novel characteristic(s)” of the claimed invention. In re Herz, 537 F.2d 549, 551-52, 190 USPQ 461, 463 (CCPA 1976). “A consisting essentially of' claim

occupies a middle ground between closed claims that are written in a consisting of' format and fully open claims that are drafted in a comprising' format." PPG Industries v. Guardian Industries, 156 F.3d 1351, 1354, 48 USPQ2d 1351, 1353-54 (Fed. Cir. 1998). See also Atlas Powder v. E.I. duPont de Nemours & Co., 750 F.2d 1569, 224 USPQ 409 (Fed. Cir. 1984); In re Janakirama-Rao, 317 F.2d 951, 137 USPQ 893 (CCPA 1963); Water Technologies Corp. vs. Calco, Ltd., 850 F.2d 660, 7 USPQ2d 1097 (Fed. Cir. 1988). For art purposes, "the consisting essentially of" language in the claim is treated as "comprising" language and it is an applicant's burden to establish that a step practiced in a prior art method is excluded from his claims by consisting essentially of' language." (See MPEP 2111.03)

Claim 7 is rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-5 of U.S. Patent No. 5942508 in view of Chen et al. (US 6383471), as applied to claims 1, 4-5, 8, 13-14, 19-20, 22, and 27 above and further in view of Fukahori et al. (JP 402083323A). Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims are drawn to an aqueous solution comprising a pyridonecarboxylic acid selected from the group consisting of lomefloxacin, norfloxacin, enoxacin, ofloxacin, ciprofloxacin, tosufloxacin, fleroxacin, cinoxacin, levofloxacin and sparfloxacin or a pharmacologically acceptable salt thereof in a concentration of 0.2-5.0 (w/v)%, and an arylcarboxylic acid selected from the group consisting of pranoprofen, ibuprofen, bromfenac, 2-naphthoic acid, 2-naphthylacetic acid and 2-naphthoxyacetic acid or a pharmacologically acceptable salt thereof in a proportion of 0.001-50 parts by weight

per part by weight of the pyridonecarboxylic acid whereas the claims herein are drawn to an aqueous liquid preparation comprising 2-amino-3-(4- bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof, and an alkyl aryl polyether alcohol type polymer or a polyethylene glycol fatty acid ester.

U.S. Patent No. 5942508 and Chen et al. (US 6383471) are discussed above.

U.S. Patent No. 5942508 and Chen et al. (US 6383471) fail to teach the amount of the polyethylene glycol as claimed.

Fukahori et al. teaches a stable aqueous solution of riboflavin containing non-ionic surfactants preferably polyoxyethylene hardened castor oil or polyethylene glycol monostearate in an amount of 0.01 to 5.0 wt %/vol%.

In the absence of showing the criticality, the determination of optimal or workable concentration of the polyethylene glycol monostearate by routine experimentation is obvious absent showing of criticality of the claimed concentration. One having ordinary skill in the art would have been motivated to do this to obtain the **desired stability and solubilizing** properties of the composition. Hence, a skilled artisan would have had reasonable expectation of successfully producing a composition with the polyethylene glycol monostearate in the claimed range.

Claims 9-10, 21, and 23-25 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-3 and 5-6 of U.S. Patent No. 5942508 in view of Chen et al. (US 6383471), as applied to claims 1, 4-

5, 8, 13-14, 19-20, 22, and 27 above and further in view of Gamache et al. (WO 01/15677) and Yakuji Nippo Ltd., ("New Drugs in Japan: 2001", 2001 Edition, Published by May 11, 2001, p.27-29 - IDS). Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims are drawn to an aqueous solution comprising a pyridonecarboxylic acid selected from the group consisting of lomefloxacin, norfloxacin, enoxacin, ofloxacin, ciprofloxacin, tosufloxacin, fleroxacin, cinoxacin, levofloxacin and sparfloxacin or a pharmacologically acceptable salt thereof in a concentration of 0.2-5.0 (w/v)%, and an arylcarboxylic acid selected from the group consisting of pranoprofen, ibuprofen, bromfenac, 2-naphthoic acid, 2-naphthylacetic acid and 2-naphthoxyacetic acid or a pharmacologically acceptable salt thereof in a proportion of 0.001-50 parts by weight per part by weight of the pyridonecarboxylic acid whereas the claims herein are drawn to an aqueous liquid preparation comprising 2-amino-3-(4- bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof, and an alkyl aryl polyether alcohol type polymer or a polyethylene glycol fatty acid ester.

U.S. Patent No. 5942508 and Chen et al. (US 6383471) are discussed above.

U.S. Patent No. 5942508 and Chen et al. (US 6383471) fail to teach the specified preservative and stabilizer; or salt and hydrate.

Gamache et al. teaches anti-inflammatory agents include bromfenac and Moxifloxacin, viscosity building agents include, for example, polyvinyl alcohol, polyvinyl pyrrolidone, methyl cellulose, hydroxypropyl methylcellulose, hydroxyethyl cellulose,

carboxymethyl cellulose, hydroxypropyl cellulose or other agents known to those skilled in the art. An appropriate buffer system (e. g., sodium phosphate, sodium acetate or sodium borate) may be added to prevent pH drift under storage conditions. Exemplified is an otic/nasal suspension: Ingredient 1B/1 D agonist 0.1-1.0% w/v, Moxifloxacin 0.3% w/v, Benzalkonium Chloride 0.01% w/v, Edetate Disodium, USP 0.01% w/v, Sodium Chloride, USP 0.3% w/v, Sodium Sulfate, USP 1.2% w/v, Tyloxapol, USP 0.05% w/v, Hydroxyethylcellulose 0.25% w/v, Sulfuric Acid and/or Sodium Hydroxide, NF q. s., and purified water q. s. to 100%.

Yakuji Nippo Ltd. teaches an aqueous ophthalmic solution comprising bromfenac sodium hydrate boric acid, sodium sulfite, disodium edetate, polyvinylpyrroldione, benzalkonium sodium hydrate.

It would have been obvious to one of ordinary skill in the art at the time of the invention to use the specific preservative Benzalkonium Chloride and stabilizer - sodium sulfite. The motivation comes from the teaching of Gamache et al. that the preservatives inclusive of Benzalkonium Chloride prevent microbial contamination during use and the stabilizer prevent pH drift under storage conditions and further by Yakuji Nippo Ltd. that an ophthalmic solution of bromfenac sodium hydrate comprises boric acid, sodium sulfite, disodium edetate, polyvinylpyrroldione, benzalkonium sodium hydrate. Hence, a skilled artisan would have had reasonable expectation of successfully producing a composition with similar efficacy and results.

Claims 11 and 12 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-3 and 5-6 of U.S. Patent No.

5942508 in view of Chen et al. (US 6383471), as applied to claims 1, 4-5, 8, 11-14, 19-20, 22, and 27 above and further in view of Sawa (20010056098). Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims are drawn to an aqueous solution comprising a pyridonecarboxylic acid selected from the group consisting of lomefloxacin, norfloxacin, enoxacin, ofloxacin, ciprofloxacin, tosufloxacin, fleroxacin, cinoxacin, levofloxacin and sparfloxacin or a pharmacologically acceptable salt thereof in a concentration of 0.2-5.0 (w/v)%, and an arylcarboxylic acid selected from the group consisting of pranoprofen, ibuprofen, bromfenac, 2-naphthoic acid, 2-naphthylacetic acid and 2-naphthoxyacetic acid or a pharmacologically acceptable salt thereof in a proportion of 0.001-50 parts by weight per part by weight of the pyridonecarboxylic acid whereas the claims herein are drawn to an aqueous liquid preparation comprising 2-amino-3-(4- bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof, and an alkyl aryl polyether alcohol type polymer or a polyethylene glycol fatty acid ester.

U.S. Patent No. 5942508 and Chen et al. (US 6383471) are discussed above.

U.S. Patent No. 5942508 and Chen et al. (US 6383471) fails to teach the pH range claimed.

Sawa teaches an aqueous solution which contains an arylcarboxylic acid or a pharmacologically acceptable salt thereof, particularly pranoprofen, dicrofenac or bromfenac, and which has sufficient stability at lower temperatures[0004]. Examples of the solubilizer include non-ionic surfactants such as polyoxyethylenesorbitan

monoolate, polyoxyethyleneoxystearic acid triglyceride, polyethylene glycol, polyoxyethylene hydrogenated castor oil and the like, [0147]. The aqueous solution of the present invention is used as an eye drop, nasal drop or ear drop. When it is used as an eye drop, its pH is generally adjusted to about 3.5-8.5, preferably about 6-8, when it is used as a nasal drop, its pH is generally adjusted to about 3.5-8.5, preferably about 6-8. Examples of the antiseptic include quaternary ammonium salts such as benzalkonium chloride. Examples of the thickener include polyvinylpyrrolidone, Examples of the chelating agent include sodium edetate, pH adjusting agents include sodium hydroxide, the reference teaches boric acid.

It would have been obvious to one of ordinary skill in the art to use a preservative or specifically - benzalkonium chloride, making the pH range claimed, and a nasal drop. The motivation comes from the teaching of Sawa that a an aqueous solution comprising bromfenac and non-ionic surfactants comprise benzalkonium chloride for its antiseptic properties; the formlation are present as eye drop, nasal drop or ear drop. When it is used as an eye drop, its pH is generally adjusted to about 3.5-8.5, preferably about 6-8, when it is used as a nasal drop, its pH is generally adjusted to about 3.5-8.5, preferably about 6-8. Hence, a skilled artisan would have reasonable expectation of successfully producing a composition with similar efficacy and results.

Claim 16 is rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-3 and 5-6 of U.S. Patent No. 5942508 in view of Chen et al. (US 6383471) and Fukahori et al. (JP 402083323A), as applied to

claims 1, 4-5, 7-8, 13-14, 19-20, 22, and 27 above and further in view of Aikawa et al. (JP 2002308764 A). Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims are drawn to an aqueous solution preparation according to claim 1, wherein the concentration of the aminoglycoside antibiotic or its pharmacologically acceptable salt in the aqueous solution preparation is within a range from a minimum of 0.01 w/v % to a maximum of 35.0 w/v %, and the concentration of the bromfenac or its pharmacologically acceptable salt in the aqueous solution preparation is within a range from a minimum of 0.01 w/v % to a maximum of 0.5 w/v %; further comprising at least one compound selected from the group consisting of a nonionic water-soluble polymer and a nonionic surfactant whereas the claims herein are drawn to an aqueous liquid preparation comprising 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof, and an alkyl aryl polyether alcohol type polymer or a polyethylene glycol fatty acid ester.

U.S. Patent No. 5942508, Chen et al. (US 6383471), and Fukahori et al. (JP 402083323A) are discussed above.

U.S. Patent No. 5942508 and Chen et al. (US 6383471), and Fukahori et al. (JP 402083323A) fail to teach the specified sodium salt or a hydrate.

Aikawa et al. teaches ophthalmic pharmaceutical composition (eye drop) for treating or preventing congestion symptom of a conjunctiva, contains bromfenac sodium hydrate.

It would have been obvious to one of ordinary skill in the art to use the sodium salt and hydrate of bromfenac. The motivation comes from the teaching of Aikawa et al. that an aqueous solution (eye drop) comprising bromfenac sodium hydrate treats or prevents congestion symptom of a conjunctiva. Hence, a skilled artisan would have reasonable expectation of successfully producing a composition with similar efficacy and results.

Claims 1, 4-5, 8, 10-12, 19-20, 22, and 27 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 5, and 47-48 of copending Application No. 11755662 in view of Chen et al. (US 6383471). Although the conflicting claims are not identical, they are not patentably distinct from each other because the copending application is drawn to a method of treating pain and/or inflammation associated with an ocular disease, injury or disorder comprising administering to a patient, in need of such treatment, a stabilized aqueous liquid solution comprising 2-amino-3-(4-bromobenzoyl) phenylacetic acid or a pharmaceutically acceptable salt thereof or a hydrate thereof at a concentration ranging from 0.05% to 0.1% administered once or twice a day, or at a concentration ranging from 0.12% to 0.24% administered once a day, and an alkyl aryl polyether alcohol type polymer whereas the claims herein are drawn to an aqueous liquid preparation comprising 2-amino-3-(4- bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof, and an alkyl aryl polyether alcohol type polymer or a polyethylene glycol fatty acid ester.

Although, the reference teaches 2-amino-3-(4-bromobenzoyl)phenalyacetic acid and a carrier the reference fails to specify an example and the specific elected species of the surfactant.

Chen et al. teaches 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). 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). 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

It would have been obvious to one of ordinary skill in the art to use a hydrophobic therapeutic agent, bromfenac, with the elected surfactant. The motivation comes from the teaching of Chen et al. that a variety of PEG-fatty acid esters have useful surfactant properties. Among the PEG-fatty acid monoesters, esters of lauric acid, oleic acid, and stearic acid are most useful. Hence, a skilled artisan would have reasonable expectation of successfully producing a composition with the most useful surfactant properties.

With respect to claim 19, the transitional phrase “consisting essentially of” limits the scope of a claim to the specified materials or steps “and those that do not materially affect the basic and novel characteristic(s)” of the claimed invention. In re Herz, 537 F.2d 549, 551-52, 190 USPQ 461, 463 (CCPA 1976). “A consisting essentially of' claim occupies a middle ground between closed claims that are written in a consisting of' format and fully open claims that are drafted in a comprising' format.” PPG Industries v. Guardian Industries, 156 F.3d 1351, 1354, 48 USPQ2d 1351, 1353-54 (Fed. Cir. 1998). See also Atlas Powder v. E.I. duPont de Nemours & Co., 750 F.2d 1569, 224 USPQ

409 (Fed. Cir. 1984); In re Janakirama-Rao, 317 F.2d 951, 137 USPQ 893 (CCPA 1963); Water Technologies Corp. vs. Calco, Ltd., 850 F.2d 660, 7 USPQ2d 1097 (Fed. Cir. 1988). For art purposes, “the consisting essentially of” language in the claim is treated as “comprising” language and it is an applicant's burden to establish that a step practiced in a prior art method is excluded from his claims by consisting essentially of' language.” (See MPEP 2111.03)

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim 7 is rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 5, and 47-48 of copending Application No. 11755662 in view of Chen et al. (US 6383471), as applied to claims 1, 4-5, 8, 10-12, 19-20, 22, and 27 above and further in view of Fukahori et al. (JP 402083323A). Although the conflicting claims are not identical, they are not patentably distinct from each other because the copending application is drawn to a method of treating pain and/or inflammation associated with an ocular disease, injury or disorder comprising administering to a patient, in need of such treatment, a stabilized aqueous liquid solution comprising 2-amino-3-(4-bromobenzoyl) phenylacetic acid or a pharmaceutically acceptable salt thereof or a hydrate thereof at a concentration ranging from 0.05% to 0.1% administered once or twice a day, or at a concentration ranging from 0.12% to 0.24% administered once a day, and an alkyl aryl polyether alcohol type polymer whereas the claims herein are drawn to an aqueous liquid preparation comprising 2-amino-3-(4- bromobenzoyl)phenylacetic acid or a pharmacologically

acceptable salt thereof or a hydrate thereof, and an alkyl aryl polyether alcohol type polymer or a polyethylene glycol fatty acid ester.

Copending Application No. 11755662 and Chen et al. (US 6383471) are discussed above.

Copending Application No. 11755662 and Chen et al. (US 6383471) fail to teach the amount of the polyethylene glycol as claimed.

Fukahori et al. teaches a stable aqueous solution of riboflavin containing non-ionic surfactants preferably polyoxyethylene hardened castor oil or polyethylene glycol monostearate in an amount of 0.01 to 5.0 wt %/vol%.

In the absence of showing the criticality, the determination of optimal or workable concentration of the polyethylene glycol monostearate by routine experimentation is obvious absent showing of criticality of the claimed concentration. One having ordinary skill in the art would have been motivated to do this to obtain the **desired stability and solubilizing** properties of the composition. Hence, a skilled artisan would have had reasonable expectation of successfully producing a composition with the polyethylene glycol monostearate in the claimed range.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 9-10, 13, 21, and 23-25 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 5, and 47-48

of copending Application No. 11755662 in view of Chen et al. (US 6383471), as applied to claims 1, 4-5, 8, 10-12, 19-20, 22, and 27 above and further in view of Gamache et al. (WO 01/15677) and Yakuji Nippo Ltd., ("New Drugs in Japan: 2001", 2001 Edition, Published by May 11, 2001, p.27-29 - IDS). Although the conflicting claims are not identical, they are not patentably distinct from each other because the copending application is drawn to a method of treating pain and/or inflammation associated with an ocular disease, injury or disorder comprising administering to a patient, in need of such treatment, a stabilized aqueous liquid solution comprising 2-amino-3-(4-bromobenzoyl) phenylacetic acid or a pharmaceutically acceptable salt thereof or a hydrate thereof at a concentration ranging from 0.05% to 0.1% administered once or twice a day, or at a concentration ranging from 0.12% to 0.24% administered once a day, and an alkyl aryl polyether alcohol type polymer whereas the claims herein are drawn to an aqueous liquid preparation comprising 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof, and an alkyl aryl polyether alcohol type polymer or a polyethylene glycol fatty acid ester.

Copending Application No. 11755662 and Chen et al. (US 6383471) are discussed above.

Copending Application No. 11755662 and Chen et al. (US 6383471) fail to teach the specified preservative and stabilizer; and sodium salts and hydrates thereof; or an eye drop.

Gamache et al. teaches anti-inflammatory agents include bromfenac and Moxifloxacin, viscosity building agents include, for example, polyvinyl alcohol, polyvinyl pyrrolidone, methyl cellulose, hydroxypropyl methylcellulose, hydroxyethyl cellulose, carboxymethyl cellulose, hydroxypropyl cellulose or other agents known to those skilled in the art. An appropriate buffer system (e. g., sodium phosphate, sodium acetate or sodium borate) may be added to prevent pH drift under storage conditions. Exemplified is an otic/nasal suspension: Ingredient 1B/1 D agonist 0.1-1.0% w/v, Moxifloxacin 0.3% w/v, Benzalkonium Chloride 0.01% w/v, Edetate Disodium, USP 0.01% w/v, Sodium Chloride, USP 0.3% w/v, Sodium Sulfate, USP 1.2% w/v, Tyloxapol, USP 0.05% w/v, Hydroxyethylcellulose 0.25% w/v, Sulfuric Acid and/or Sodium Hydroxide, NF q. s., and purified water q. s. to 100%.

Yakuji Nippo Ltd. teaches an aqueous ophthalmic solution comprising bromfenac sodium hydrate boric acid, sodium sulfite, disodium edetate, polyvinylpyrroldione, benzalkonium sodium hydrate.

It would have been obvious to one of ordinary skill in the art at the time of the invention to use the specific preservative Benzalkonium Chloride and stabilizer - sodium sulfite. The motivation comes from the teaching of Gamache et al. that the preservatives inclusive of Benzalkonium Chloride prevent microbial contamination during use and the stabilizer prevent pH drift under storage conditions and further by Yakuji Nippo Ltd. that an ophthalmic solution of bromfenac sodium hydrate comprises boric acid, sodium sulfite, disodium edetate, polyvinylpyrroldione, benzalkonium sodium hydrate. Hence, a

skilled artisan would have had reasonable expectation of successfully producing a composition with similar efficacy and results.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim 14 is rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 5, and 47-48 of copending Application No. 11755662 in view of Chen et al. (US 6383471), as applied to claims 1, 4-5, 8, 10-12, 19-20, 22, and 27 above and further in view of Sawa (5942508). Although the conflicting claims are not identical, they are not patentably distinct from each other because the copending application is drawn to a method of treating pain and/or inflammation associated with an ocular disease, injury or disorder comprising administering to a patient, in need of such treatment, a stabilized aqueous liquid solution comprising 2-amino-3-(4-bromobenzoyl) phenylacetic acid or a pharmaceutically acceptable salt thereof or a hydrate thereof at a concentration ranging from 0.05% to 0.1% administered once or twice a day, or at a concentration ranging from 0.12% to 0.24% administered once a day, and an alkyl aryl polyether alcohol type polymer whereas the claims herein are drawn to an aqueous liquid preparation comprising 2-amino-3-(4- bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof, and an alkyl aryl polyether alcohol type polymer or a polyethylene glycol fatty acid ester.

Copending Application No. 11755662 and Chen et al. (US 6383471) are discussed above.

Copending Application No. 11755662 and Chen et al. (US 6383471) fails to a nose drop.

Sawa teaches an aqueous solution comprising a pyridonecarboxylic acid selected from the group consisting of lomefloxacin, norfloxacin, enoxacin, ofloxacin, ciprofloxacin, tosufloxacin, fleroxacin, cinoxacin, levofloxacin and sparfloxacin or a pharmacologically acceptable salt thereof in a concentration of 0.2-5.0 (w/v)%, and an arylcarboxylic acid selected from the group consisting of pranoprofen, ibuprofen, bromfenac, 2-naphthoic acid, 2-naphthylacetic acid and 2-naphthoxyacetic acid or a pharmacologically acceptable salt thereof in a proportion of 0.001-50 parts by weight per part by weight of the pyridonecarboxylic acid (see claim 2). The reference further teaches examples of the solubilizer include non-ionic surfactants such as polyoxyethylenesorbitane monoolate, polyoxyethyleneoxystearic acid triglyceride, polyethylene glycol, polyoxyethylene hydrogenated castor oil and the like, (col 8 lines 66-67 and col 9 lines 1-3). The aqueous solution of the present invention is used as an eye drop, nasal drop or ear drop. When it is used as an eye drop, its pH is generally adjusted to about 3.5-8.5, preferably about 6-8, when it is used as a nasal drop, its pH is generally adjusted to about 3.5-8.5, preferably about 6-8, (See claims 3-5). Examples of the antiseptic include quaternary ammonium salts such as benzalkonium chloride. Examples of the thickener include polyvinylpyrrolidone, Examples of the chelating agent

include sodium edetate, pH adjusting agents include sodium hydroxide, the reference teaches boric acid.

It would have been obvious to one of ordinary skill in the art to use the formulation as a nasal drop. The motivation comes from the teaching of Sawa that an aqueous solution comprising bromfenac is used as an eye drop, nasal drop or ear drop. When it is used as an eye drop, its pH is generally adjusted to about 3.5-8.5, preferably about 6-8, when it is used as a nasal drop, its pH is generally adjusted to about 3.5-8.5, preferably about 6-8. Hence, a skilled artisan would have reasonable expectation of successfully producing a composition with similar efficacy and results.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim 16 is rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 5, and 47-48 of copending Application No. 11755662 in view of Chen et al. (US 6383471) and Fukahori et al. (JP 402083323A), as applied to claims 1, 4-5, 7-8, 10-12, 19-20, 22, and 27 above and further in view of Aikawa et al. (JP 2002308764 A). Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims are drawn to an aqueous solution preparation according to claim 1, wherein the concentration of the aminoglycoside antibiotic or its pharmacologically acceptable salt in the aqueous solution preparation is within a range from a minimum of 0.01 w/v % to a maximum of 35.0 w/v %, and the concentration of the bromfenac or its

pharmacologically acceptable salt in the aqueous solution preparation is within a range from a minimum of 0.01 w/v % to a maximum of 0.5 w/v %; further comprising at least one compound selected from the group consisting of a nonionic water-soluble polymer and a nonionic surfactant whereas the claims herein are drawn to an aqueous liquid preparation comprising 2-amino-3-(4- bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof, and an alkyl aryl polyether alcohol type polymer or a polyethylene glycol fatty acid ester.

U.S. Patent No. 5942508, Chen et al. (US 6383471), and Fukahori et al. (JP 402083323A) are discussed above.

U.S. Patent No. 5942508 and Chen et al. (US 6383471), and Fukahori et al. (JP 402083323A) fail to teach the specified sodium salt or a hydrate.

Aikawa et al. teaches ophthalmic pharmaceutical composition (eye drop) for treating or preventing congestion symptom of a conjunctiva, contains bromfenac sodium hydrate.

It would have been obvious to one of ordinary skill in the art to use the sodium salt and hydrate of bromfenac. The motivation comes from the teaching of Aikawa et al. that an aqueous solution (eye drop) comprising bromfenac sodium hydrate treats or prevents congestion symptom of a conjunctiva. Hence, a skilled artisan would have reasonable expectation of successfully producing a composition with similar efficacy and results.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

The arguments are not persuasive and the rejection is made **FINAL**.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Conclusion

No claims allowed.

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 Monday through Friday from 8:30 a.m. to 5:00 p.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).

/Layla Soroush/

Examiner, Art Unit 1627

Search Notes	Application/Control No.	Applicant(s)/Patent under Reexamination	
	13/353,653	SAWA ET AL.	
	Examiner	Art Unit	
	LAYLA SOROUSH	1627	

SEARCHED			
Class	Subclass	Date	Examiner

INTERFERENCE SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES (INCLUDING SEARCH STRATEGY)		
	DATE	EXMR
SAWA, SHIROU FUJITA, SHUHEI	5/6/2013	LS
PEG and bromfenac	5/6/2013	LS

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Named Inventor	:	Attorney Docket No. 2012_0088
Shirou SAWA	:	**Confirmation No. 1077**
Serial No. 13/353,653	:	Group Art Unit 1627
Filed January 19, 2012	:	Examiner Layla Soroush
AQUEOUS LIQUID PREPARATION CONTAINING 2-AMINO-3-(4-BROMOBENZOYL)PHENYLACETIC ACID	:	**Mail Stop: AMENDMENT**

AMENDMENT

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

Sir:

Responsive to the Official Action dated August 30, 2012, the time for responding thereto being extended for two months in accordance with payment of the PTO extension fee submitted concurrently herewith, please amend the above-identified application as follows:

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.

Amendments to the Claims

1. (Currently amended) An aqueous liquid preparation comprising 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a ~~pharmacologically acceptable~~ sodium salt thereof or a hydrate thereof, and ~~an alkyl aryl polyether alcohol type polymer or~~ a polyethylene glycol fatty acid ester, ~~provided that the alkyl aryl polyether alcohol type polymer is not tyloxapol~~ wherein

the concentration of the polyethylene glycol fatty acid ester is selected from a range of a minimum concentration of 0.02 w/v % to a maximum concentration of 0.1 w/v%.

2-3. (Canceled)

4. (Original) The aqueous liquid preparation according to claim 1, wherein the carbon number of the fatty acid in the polyethylene glycol fatty acid ester is 12 to 18.

5. (Previously presented) The aqueous liquid preparation according to claim 1, wherein the polyethylene glycol fatty acid ester is polyethylene glycol monostearate.

6-7. (Canceled)

8. (Currently amended) The aqueous liquid preparation according to claim 1, wherein the concentration of the 2-amino-3-(4-bromobenzoyl)phenylacetic acid or ~~a pharmacologically acceptable~~ the sodium salt thereof or ~~a~~ the hydrate thereof is 0.01 to 0.5 w/v %.

9. (Previously presented) The aqueous liquid preparation according to claim 1, wherein benzalkonium chloride is contained as a preservative.

10. (Canceled)

11. (Previously presented) The aqueous liquid preparation according to claim 1, wherein the pH of the aqueous liquid preparation is within a range of 7 to 9.

12. (Original) The aqueous liquid preparation according to claim 11, wherein the pH of the aqueous liquid preparation is within a range of 7.5 to 8.5.

13. (Previously presented) The aqueous liquid preparation according to claim 1, wherein the aqueous liquid preparation is an eye drop.

14. (Previously presented) The aqueous liquid preparation according to claim 1, wherein the aqueous liquid preparation is a nasal drop.

15. (Canceled)

16. (Original) An eye drop comprising sodium 2-amino-3-(4-bromobenzoyl)phenylacetate hydrate and 0.02 to 0.1 w/v % of polyethylene glycol monostearate.

17. (Currently amended) A method for stabilizing 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a ~~pharmacologically acceptable~~ sodium salt thereof or a hydrate thereof in an aqueous liquid preparation, which comprises incorporating ~~tyloxapol or~~ polyethylene glycol monostearate into an aqueous liquid preparation containing 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a ~~pharmacologically acceptable~~ sodium salt thereof or a hydrate thereof.

18. (Currently amended) A method for inhibiting decrease in preservative effect of a preservative in an aqueous liquid preparation of 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a ~~pharmacologically acceptable~~ sodium salt thereof or a hydrate thereof, which comprises incorporating tyloxapol or polyethylene glycol monostearate into an aqueous liquid preparation containing 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a ~~pharmacologically acceptable~~ sodium salt thereof or a hydrate thereof and a preservative.

19. (Currently amended) The aqueous liquid preparation according to claim 1, which consists essentially of the following two components, wherein the first component is the 2-

amino-3-(4- bromobenzoyl)phenylacetic acid or ~~a pharmacologically acceptable~~ the sodium salt thereof or ~~a~~ the hydrate thereof, and the second component is ~~the alkyl aryl polyether alcohol type polymer or~~ the polyethylene glycol fatty acid ester.

20. (Previously presented) The aqueous liquid preparation according to claim 1, which is formulated for ophthalmic administration.

21. (Previously presented) The aqueous liquid preparation according to claim 1, wherein when a quaternary ammonium compound is included in said liquid preparation, the quaternary ammonium compound is benzalkonium chloride.

22. (Previously presented) The aqueous liquid preparation according to claim 1, which further includes one or more additives selected from the group consisting of a preservative, buffer, thickener, stabilizer, chelating agent, and pH controlling agent.

23. (Currently amended) The aqueous liquid preparation according to claim ~~1~~ 22, wherein said preservative is benzalkonium chloride; wherein said buffer is boric acid and/or sodium borate; wherein said thickener is polyvinylpyrrolidone; wherein said stabilizer is sodium sulfite; wherein said chelating agent is sodium edetate; and wherein said pH controlling agent is sodium hydroxide.

24. (Previously presented) The aqueous liquid preparation according to claim 1, wherein the concentration of the 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt is about 0.2 w/v %.

25. (Previously presented) The aqueous liquid preparation according to claim 1, wherein the hydrate is at least one selected from a 1/2 hydrate, 1 hydrate and 3/2 hydrate.

26-27. (Canceled)

28. (New) The aqueous liquid preparation according to claim 1 wherein the polyethylene glycol fatty acid ester is polyoxyl 40 stearate.

REMARKS

Favorable reconsideration is respectfully requested in view of the foregoing amendments and following remarks.

I. Examiner Interview

The Applicants express their sincere appreciation to the Examiner and her supervisor for their courtesy and helpful suggestions made during the telephone interview held on December 5, 2012.

The claims and the various grounds of rejection were reviewed. The Examiners recommended that in order to expedite allowance, the Applicant submit evidence of unexpected stabilizing effects of the claimed polyethylene glycol fatty acid esters on bromfenac.

II. Claim Amendments

Claim 1 is amended by incorporating the subject matter of claims 7, 10 and 27.

The claimed salt is limited to a sodium salt. Support is found for example in Experimental Example 1 on page 14 of the specification.

Claims 2, 6, 7, 10, 26 and 27 are canceled without prejudice.

New claim 28 is presented for additional patent protection based upon page 10, line 14 of the specification.

III. Rejection under 35 U.S.C. §112

Claim 23 is rejected as lacking antecedent basis based upon claim 1. Claim 23 has been amended to correct the dependency upon claim 22.

Thus this ground of rejection is deemed to be overcome.

IV. Characteristics of the Present Invention

The present invention is characterized by the combination of the following limitations:

(1) an aqueous liquid preparation;

(2) 2-amino-3-(4-bromobenzoyl) phenylacetatic acid or a sodium salt thereof or a hydrate thereof;

(3) a polyethylene glycol fatty acid ester; and

(4) the concentration of the polyethylene glycol fatty acid ester is selected from a range of a minimum concentration of 0.02 w/v% to a maximum concentration of 0.1 w/v%.

V. Unexpected Effects of the Present Invention

On the basis of the specific combination of limitations (1) to (4), the present invention shows excellent effects in that (1) the aqueous liquid preparation is stable within a pH range giving no irritation to eyes; and (2) the change of the 2-amino-3- (4-bromobenzoyl) phenylacetic acid over time can be inhibited, (c.f. page 4, lines 11-14 of the specification).

These excellent effects are clearly demonstrated by Experiments 1 to 3 of Rule 1.132 Declaration executed by Mr. Shirou Sawa enclosed herewith. Experiments 1 to 3 of Rule 1.132 Declaration respectively correspond to Experimental Examples 1 to 3 of the present specification (however, please be advised that Table 3 of the Rule 1.132 Declaration corresponds to Table 3-3 in the present specification).

Experiment 1

Stability of sodium 2-amino-3-(4-bromobenzoyl)phenylacetate 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°C for 4 weeks.

Table 1

Component	Comparison Example 1	A-01
Sodium 2-amino-3-(4-bromobenzoyl)phenylacetate	0.1 g	0.1 g
Boric acid	1.5 g	1.5 g
Benzalkonium chloride	0.005 g	0.005 g
Polysorbate 80	0.15 g	-
Polyoxyl 40 stearate	-	0.15 g
Tyloxapol	-	-
Sterile purified water	q.s.	q.s.
Total volume	100 mL	100 mL
pH	7.0	7.0
Remaining rate (%) of sodium 2-amino-3-(4-bromobenzoyl) phenylacetate at 60 °C after 4 weeks	51.3	63.7

As is apparent from Table 1, the stability test was carried out under the conditions of pH 7.0 at 60°C 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.

Experiment 2

Stability of sodium 2-amino-3-(4-bromobenzoyl)phenylacetate was evaluated. Namely, two eye drops of sodium 2-amino-3-(4-bromobenzoyl)phenylacetate comprising the components as shown in Table 2 were prepared, and filled respectively into a polypropylene container and preserved at 60°C for 4 weeks.

Table 2

Components		A—07	A—08
Sodium 2-amino-3-(4-bromobenzoyl)phenyl-acetate		0.1 g	0.1 g
Boric acid		1.1 g	1.1 g
Borax		1.1 g	1.1 g
Benzalkonium chloride		0.005g	0.005g
Polyoxyl 40 stearate		0.02 g	0.05 g
Polyvinyl-pyrrolidone (K-30)		2.0 g	1.0 g
Sodium edetate		0.02 g	0.02 g
Sodium hydroxide		q.s.	q.s.
Sterile purified water		q.s.	q.s.
Total volume		100 mL	100 mL
pH		8.19	8.19
60°C, 4 weeks	Remaining rate (%)	93.4	93.1
	pH	8.13	8.14

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°C 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.

Experiment 3

Preservative effect test of composition A-07 of Experiment 2 was carried out against *Staphylococcus aureus* (referred to as *S. aureus*), *Escherichia Coli* (referred to as *E. coli*),

Pseudomonas aeruginosa (referred to as *P. aeruginosa*), *Candida albicans* (referred to as *C. albicans*) and *Aspergillus niger* (referred to as *A. niger*).

The results are shown in Table 3.

Table 3

A—07	Cell count (CFU/mL)						
	Inoculum count	6 hours after inocula-tion	24 hours after inocula-tion	7 days after inocula-tion	14 days after inocula-tion	21 days after inocula-tion	28 days after inocula-tion
S. aureus	2.7×10^6	3.1×10^4	0	0	0	0	0
E. coli	7.4×10^6	0	0	0	0	0	0
P. aeruginosa	8.8×10^6	0	0	0	0	0	0
C. albicans	4.6×10^5	—	—	0	0	0	0
A. niger	1.0×10^5	—	—	0	0	0	0

As is apparent from Table 3, the preservative effect of the composition containing 0.02 w/v % of polyoxyl 40 stearate was found to be compatible with EP-criteria B in the European Pharmacopoeia (EP).

The EP-criteria B are given in the following.

EP-criteria B:

Viable cell counts of bacteria (*S. aureus, P. aeruginosa*) 24 hours and 7 days after inoculation decrease to not more than 1/10 and not more than 1/1000, respectively, and thereafter, the cell count levels off or decreases. Viable cell count of fungi (*C. albicans, A. niger*) 14 days after inoculation decreases to not more than 1/10, and thereafter, the cell count keeps the same level as that of 14 days after inoculation.

These effects are unexpectedly excellent over the compositions of the cited references.

Accordingly, the present invention is unobvious over the cited references to a person skilled in the art.

VI. Obviousness Rejection of Claims 1, 4-5, 8, 19-20, 22 and 27 under 35 U.S.C. §103 Over Chen et al.

As mentioned above, amended claim 1 is made by restricting claim 1 with claims 7, 10 and 27.

Amended claims 4-5, 8, 19-20 and 22 are dependent upon amended claim 1.

Amended claim 1 is made by incorporating non-rejected claims 7 and 10.

Accordingly, the present rejection will be overcome.

VII. Obviousness Rejection of Claims 1, 4-5, 8-9, 11-14, 19-22 and 27 under 35 U.S.C. §103 over Sawa (U.S. 5,942,508) in View of Chen et al.

Amended claims 4-5, 8-9, 11-14 and 19-22 are dependent upon amended claim 1.

Amended claim 1 is made by incorporating non-rejected claims 7 and 10.

Accordingly, the present rejection will be overcome.

VIII. Obviousness Rejection of Claims 1, 4-5, 8-9, 11-14, 19-22 and 27 under 35 U.S.C. §103 over Sawa (U. S. 6,274,592) in View of Chen et al.

Amended claims 4-5, 8-9, 11-14 and 19-22 are dependent upon amended claim 1.

Amended claim 1 is made by incorporating non-rejected claims 7 and 10.

Accordingly, the present rejection will be overcome.

IX. Obviousness Rejection of Claims 1, 4-5, 8-9, 11-14, 19-22 and 27 under 35 U.S.C. §103 Over Sawa (U.S. 2001/0056098) in View of Chen et al.

Amended claims 4-5, 8-9, 11-14 and 19-22 are dependent upon amended claim 1.

Amended claim 1 is made by incorporating non-rejected claims 7 and 10.

Accordingly, the present rejection will be overcome.

X. Obviousness Rejection of Claim 7 under 35 U.S.C. §103 Over Chen et al., and Further in View of Fukahori et al.

Present claim 7 is canceled, and therefore, the present rejection will be overcome.

XI. Obviousness Rejection of Claim 7 under 35 U.S.C. §103 Over Sawa '508 in View of Chen et al., and Further in View of Fukahori et al.

Claim 7 is canceled, and therefore, the present rejection will be overcome.

XII. Obviousness Rejection of Claim 7 under 35 U.S.C. §103 Over Sawa '592 in View of Chen et al., and Further in View of Fukahori et al.

Claim 7 is canceled, and therefore, the present rejection will be overcome.

XIII. Obviousness Rejection of Claim 7 Under 35 U.S.C. §103 over Sawa '098 in View of Chen et al., and Further in View of Fukahori et al.

Present claim 7 is canceled, and therefore, the present rejection will be overcome.

XIV. Obviousness Rejection of Claims 9, 11-14 and 21 under 35 U.S.C. §103 over Chen et al., and Further in View of Sawa ('508)

Amended claims 9, 11-14 and 21 are dependent upon amended claim 1.

Amended claim 1 is made by incorporating non-rejected claims 7 and 10.

Accordingly, the present rejection will be overcome.

XV. Obviousness Rejection of Claims 9, 11-14 and 21 under 35 U.S.C. §103 Over Chen et al., and Further in View of Sawa ('592)

Amended claims 9, 11-14 and 21 are dependent upon amended claim 1.

Amended claim 1 is made by incorporating non-rejected claims 7 and 10.

Accordingly, the present rejection will be overcome.

XVI. Obviousness Rejection of Claims 9, 11-14 and 21 under 35 U.S.C. §103 Over Chen et al., and Further in View of Sawa ('098)

Amended claims 9, 11-14 and 21 are dependent upon amended claim 1.

Amended claim 1 is made by incorporating non-rejected claims 7 and 10.

Accordingly, the present rejection will be overcome.

XVII. Obviousness Rejection of Claims 9, 21 and 23 under 35 U.S.C. §103 over Chen et al., and Further in View of Gamache et al. and Yakuji Nippo Ltd.

Amended claims 9, 21 and 23 are dependent upon amended claim 1.

Amended claim 1 is made by incorporating non-rejected claims 7 and 10.

Accordingly, the present rejection will be overcome.

XVIII. Obviousness Rejection of Claims 10 and 23-25 under 35 U.S.C. §103 Over Sawa '508 in View of Chen et al. and Further in View of Gamache et al. and Yakuji Nippo Ltd.

Amended claims 23 -25 are dependent upon amended claim 1.

Amended claim 1 is made by incorporating non-rejected claim 7.

Accordingly, the present rejection will be overcome.

XIX. Obviousness Rejection of Claims 10 and 23-25 under 35 U.S.C .§103 over Sawa '592 in view of Chen et al. and Further in View of Gamache et al. and Yakuji Nippo Ltd.

Amended claims 23-25 are dependent upon amended claim 1.

Amended claim 1 is made by incorporating non-rejected claim 7.

Accordingly, the present rejection will be overcome.

XX. Obviousness Rejection of Claims 10 and 23-25 under 35 U.S.C. §103 over Sawa '098 in View of Chen et al. and Further in View of Gamache et al. and Yakuji Nippo Ltd.

Amended claims 23-25 are dependent upon amended claim 1.

Amended claim 1 is made by incorporating non-rejected claim 7.

Accordingly, the present rejection will be overcome.

XXI. Obviousness Rejection of Claim 16 under 35 U.S.C. §103 over Chen et al. and Fukahori et al., and Further in View of Aikawa et al.

Amended claim 16 is dependent upon amended claim 1.

Amended claim 1 is made by incorporating non-rejected claims 7 and 10.

Accordingly, the present rejection will be overcome.

XXII. Obviousness Rejection of claim 16 under 35 U.S.C. §103 over Sawa '508 in View of Chen et al. and Fukahori et al., and Further in View of Aikawa et al.

Amended claim 16 is dependent upon amended claim 1.

Amended claim 1 is made by incorporating non-rejected claims 7 and 10.

Accordingly, the present rejection will be overcome.

XXIII. Obviousness Rejection of Claim 16 under 35 U.S.C. §103 over Sawa '592 in View of Chen et al. and Fukahori et al., and Further in View of Aikawa et al.

Amended claim 16 is dependent upon amended claim 1.

Amended claim 1 is made by incorporating non-rejected claims 7 and 10.

Accordingly, the present rejection will be overcome.

XXIV. Obviousness Rejection of Claim 16 under 35 U.S.C. §103 over Sawa '098 in View of Chen et al. and Fukahori et al., and Further in View of Aikawa et al.

Amended claim 16 is dependent upon amended claim 1.

Amended claim 1 is made by incorporating non-rejected claims 7 and 10.

Accordingly, the present rejection will be overcome.

XXV. Double Patenting

These grounds of rejection will be overcome by the amended claims.

XXVI. Conclusion

In view of the foregoing, it is believed that each ground of rejection set forth in the Official Action has been overcome, and that the application is now in condition for allowance.

Accordingly, such allowance is solicited.

Respectfully submitted,

/Warren M. Cheek/

Digitally signed by /Warren M. Cheek/
DN: cn=/Warren M. Cheek/, o, ou, email=wcheek@wenderoth.com, c=US
Date: 2013.01.30 13:54:39 -05'00'

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January 30, 2013

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of : Confirmation No. 1077
Serial No. 13/353,536 : Group Art Unit: 1627
Shirou SAWA et al. : Examiner: Layla Soroush
Filed: January 19, 2012

DECLARATION UNDER 37 CFR 1.132

Honorable Commissioner of Patent and Trademarks

Sir:

I, Shirou SAWA declare that:

I am one of inventors for the above-identified US patent application;

I am a citizen of Japan and a resident of c/o Senju Pharmaceutical Co., Ltd., 5-4, Murotani 1-chome, Nishi-ku, Kobe-shi, Hyogo 651-2241, Japan;

I graduated from Department of Chemical Engineering, Faculty of Engineering, The University of Tokushima, Tokushima, Japan in 1988;

I took the master degree on the study of the chemical engineering at The University of Tokushima, Tokushima, Japan in 1990;

I have been an employee of SENJU PHARMACEUTICAL CO., LTD., Japan, since 1990 up to this time, and have been engaged in research relating to pharmaceutics;

I am a member of the Japan society of drug delivery system since July 2001.

The experiments set out below were conducted under my supervision and direction.

Experiment 1

Stability test of sodium 2-amino-3-(4-bromobenzoyl)-phenylacetate

(1) Test Method

Two kinds of 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 stability test. Stability test was carried out under the condition of pH 7.0 at 60°C for 4 weeks.

Table 1

Component	Comparison Example 1	A-01
Sodium 2-amino-3-(4-bromobenzoyl)phenylacetate	0.1 g	0.1 g
Boric acid	1.5 g	1.5 g
Benzalkonium chloride	0.005 g	0.005 g
Polysorbate 80	0.15 g	-
Polyoxyl 40 stearate	-	0.15 g
Tyloxapol	-	-
Sterile purified water	q.s.	q.s.
Total volume	100 mL	100 mL
pH	7.0	7.0
Remaining rate (%) of sodium 2-amino-3-(4-bromobenzoyl) phenylacetate at 60 °C after 4 weeks	51.3	63.7

(2) Test Result

The remaining rate (%) of sodium 2-amino-3-(4-bromobenzoyl)phenylacetate in Table 1 indicates values obtained by correcting moisture vaporization from the container. As is apparent from Table 1, the remaining rate of sodium 2-amino-3-(4-bromobenzoyl)phenylacetate in the polyoxyl 40 stearate-containing preparation at 60°C for 4 weeks is 12.4% higher than that in the polysorbate 80-containing preparation.

Therefore, with regard to the stability of sodium 2-amino-3-(4-bromobenzoyl)phenylacetate, the polyoxyl 40 stearate-containing preparation were quite superior to the

polysorbate 80-containing preparation.

Experiment 2

Stability test of sodium 2-amino-3-(4-bromobenzoyl)-phenylacetate

(1) Test Method

Two eye drops of sodium 2-amino-3-(4-bromobenzoyl)phenylacetate comprising the components as shown in Table 2 were prepared, and filled respectively into a polypropylene container and preserved at 60°C for 4 weeks.

Table 2

Components		A—07	A—08
Sodium 2-amino-3-(4-bromobenzoyl)phenyl-acetate		0.1 g	0.1 g
Boric acid		1.1 g	1.1 g
Borax		1.1 g	1.1 g
Benzalkonium chloride		0.005g	0.005g
Polyoxyl 40 stearate		0.02 g	0.05 g
Polyvinyl-pyrrolidone (K-30)		2.0 g	1.0 g
Sodium edetate		0.02 g	0.02 g
Sodium hydroxide		q.s.	q.s.
Sterile purified water		q.s.	q.s.
Total volume		100 mL	100 mL
pH		8.19	8.19
60°C, 4 weeks	Remaining rate (%)	93.4	93.1
	pH	8.13	8.14

(2) Test Result

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°C for 4 weeks, which indicates that those compositions have sufficient stability for eye drops.

Experiment 3

Preservative effect test of compositions containing polyoxyl 40 stearate

(1) Test Method

Preservative effect test of composition A-07 as shown in Table 2 was carried out against *Staphylococcus aureus* (referred to as *S. aureus*), *Escherichia Coli* (referred to as *E. coli*), *Pseudomonas aeruginosa* (referred to as *P. aeruginosa*), *Candida albicans* (referred to as *C. albicans*) and *Aspergillus niger* (referred to as *A. niger*) as shown in Table 3.

10 mL of the sample (compositions A-07) was dispensed into 5 sterilized stoppered test tubes. Each kind of bacteria or fungi as shown in Table 3 was inoculated into one test tube of the sample so as to be a density of 10^6 CFU/mL of bacteria or a density of 10^5 CFU/mL of fungi. These test tubes of the inoculated samples were preserved at about 20-25°C. Sampling was carried out 6 hours, 24 hours, 7 days, 14 days, 21 days and 28 days after inoculation. As to the way of sampling, 0.5 mL of sample was batched off from each of the test tubes and was subjected to 10-, 100- or 1000-fold dilution by sterile physiological saline solution, followed by the inoculation into a petri dish. With regard to bacteria, 15-20 mL of soybean-casein digest agar medium containing an inactivator (0.1% of lecithin and 0.7% of polysorbate 80) was dispensed. With regard to fungi, 15-20 mL of Sabouraud glucose agar medium containing an inactivator (0.1% of lecithin and 0.7% of polysorbate 80) was dispensed. Thereafter, cultivation was carried out in the condition as shown in Table 3. Finally, viable cell count was determined.

Table 3

A—07	Cell count (CFU/mL)						
	Inoculum count	6 hours after inocula-tion	24 hours after inocula-tion	7 days after inocula-tion	14 days after inocula-tion	21 days after inocula-tion	28 days after inocula-tion
S. aureus	2.7×10^6	3.1×10^4	0	0	0	0	0
E. coli	7.4×10^6	0	0	0	0	0	0
P. aeruginosa	8.8×10^6	0	0	0	0	0	0
C. albicans	4.6×10^5	—	—	0	0	0	0
A. niger	1.0×10^5	—	—	0	0	0	0

(2) Test Result

As is apparent from Table 3, the preservative effect of composition containing 0.02 w/v % of polyoxyl 40 stearate was found to be compatible with EP-criteria B in European Pharmacopoeia (EP).

The EP-criteria B are given in the following.

EP-criteria B:

Viable cell counts of bacteria (*S. aureus, P.aeruginosa*) 24 hours and 7 days after inoculation decrease to not more than 1/10 and not more than 1/1000, respectively, and thereafter, the cell count levels off or decreases.

Viable cell count of fungi (*C. albicans, A. niger*) 14 days after inoculation decreases to not more than 1/10, and thereafter, the cell count keeps the same level as that of 14 days after inoculation.

It is declared by the undersigned that all statements made herein of undersigned's 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 18 U.S.C. 1001, and that such willful false statements may jeopardize the validity of the above-identified application or any patent issuing thereon.

This 14 day of December, 2012

Shirou Sawa

Shirou SAWA

Electronic Patent Application Fee Transmittal

Application Number:	13353653
Filing Date:	19-Jan-2012
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:	2012_0088

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:				
Extension - 2 months with $0 paid	1252	1	570	570

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
			Total in USD ($)	**570**

Electronic Acknowledgement Receipt

EFS ID:	14830525
Application Number:	13353653
International Application Number:	
Confirmation Number:	1077
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./ann leveille
Filer Authorized By:	Warren M. Cheek Jr.
Attorney Docket Number:	2012_0088
Receipt Date:	30-JAN-2013
Filing Date:	19-JAN-2012
Time Stamp:	15:33:06
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Credit Card
Payment was successfully received in RAM	$570
RAM confirmation Number	2232
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		AttachA.pdf	585804 0f7f01e3e4c9c103803491d2eaef137dae429f1f	yes	15

Multipart Description/PDF files in .zip description

Document Description	Start	End
Amendment/Req. Reconsideration-After Non-Final Reject	1	1
Claims	2	5
Applicant Arguments/Remarks Made in an Amendment	6	15

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3	Fee Worksheet (SB06)	fee-info.pdf	31097 84c839a042779802220ebd018dadc8704488eda7	no	2

Warnings:

Information:

Total Files Size (in bytes):	769426

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.

UNITED STATES PATENT AND TRADEMARK OFFICE

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/353,653	01/19/2012	Shirou Sawa	2012_0088	1077

513 7590 08/30/2012

WENDEROTH, LIND & PONACK, L.L.P.
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Washington, DC 20005-1503

EXAMINER	
SOROUSH, LAYLA	

ART UNIT	PAPER NUMBER
1627	

NOTIFICATION DATE	DELIVERY MODE
08/30/2012	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

ddalecki@wenderoth.com
eoa@wenderoth.com

Office Action Summary	Application No.	Applicant(s)	
	13/353,653	SAWA ET AL.	
	Examiner	Art Unit	
	LAYLA SOROUSH	1627	

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

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 April 2012*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ 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.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

5)☒ Claim(s) *1,2,4-14 and 16-27* is/are pending in the application.

5a) Of the above claim(s) *2,6,17,18 and 26* is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *1,4,5,7-14,16,19-25 and 27* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

12)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

13)☒ 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:

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)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/19/12*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The Office Action is in response to the Applicant's reply filed April 3, 2012 to the restriction requirement made on March 16, 2012.

Applicant's election of Group I and the species polyethylene glycol fatty acid monoester of claims 1, 4-5, 7-14, 16, 19-25 and 27 with traverse is acknowledged. Because the applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP 818.03 (a)).

The requirement is still deemed proper and is therefore made **FINAL**.

/SREENI PADMANABHAN/

Supervisory Patent Examiner, Art Unit 1627

Claims 2, 6, 17, 18, and 26 are withdrawn from further consideration pursuant to 37 C.F.R. 1.142(b), as being drawn to non-elected subject matter. The claims corresponding to the elected subject matter are 1, 4-5, 7-14, 16, 19-25 and 27; and are herein acted on the merits.

The claims are examined to the extent that they read on the elected species - polyethylene glycol fatty acid monoester.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 23 recites the limitation "said preservative; said buffer; said thickner; said stabilizer; said chelating agent said pH controlling agent" in claim 1. There is insufficient antecedent basis for this limitation in the claim. The claims are examined to the extent that they read on a composition further comprising a preservative; buffer; thickner; stabilizer; chelating agent; and pH controlling agent.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was

not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 4-5, 8, 19-20, 22, and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chen et al. (US 6383471).

Chen et al. teaches 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).

Although, the reference teaches both 2-amino-3-(4-bromobenzoyl)phenalyacetic acid and a polyethylene glycol fatty acid monoester dispersed with water, the reference fails to specify an example.

It would have been obvious to one of ordinary skill in the art to use a hydrophobic therapeutic agent, bromfenac, with a surfactant. The motivation comes from the

teaching of Chen et al. that a variety of PEG-fatty acid esters have useful surfactant properties. Among the PEG-fatty acid monoesters, esters of lauric acid, oleic acid, and stearic acid are most useful. Hence, a skilled artisan would have reasonable expectation of successfully producing a composition with the most useful surfactant properties.

With respect to claim 19, the transitional phrase “consisting essentially of” limits the scope of a claim to the specified materials or steps “and those that do not materially affect the basic and novel characteristic(s)” of the claimed invention. In re Herz, 537 F.2d 549, 551-52, 190 USPQ 461, 463 (CCPA 1976). “A consisting essentially of' claim occupies a middle ground between closed claims that are written in a consisting of' format and fully open claims that are drafted in a comprising' format.” PPG Industries v. Guardian Industries, 156 F.3d 1351, 1354, 48 USPQ2d 1351, 1353-54 (Fed. Cir. 1998). See also Atlas Powder v. E.I. duPont de Nemours & Co., 750 F.2d 1569, 224 USPQ 409 (Fed. Cir. 1984); In re Janakirama-Rao, 317 F.2d 951, 137 USPQ 893 (CCPA 1963); Water Technologies Corp. vs. Calco, Ltd., 850 F.2d 660, 7 USPQ2d 1097 (Fed. Cir. 1988). For art purposes, “the consisting essentially of” language in the claim is treated as “comprising” language and it is an applicant's burden to establish that a step practiced in a prior art method is excluded from his claims by consisting essentially of' language.” (See MPEP 2111.03)

Claims 1, 4-5, 8-9, 11-14, 19-22, and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sawa (5942508) in view of Chen et al. (US 6383471).

Sawa teaches an aqueous solution comprising a pyridonecarboxylic acid selected from the group consisting of lomefloxacin, norfloxacin, enoxacin, ofloxacin, ciprofloxacin, tosufloxacin, fleroxacin, cinoxacin, levofloxacin and sparfloxacin or a pharmacologically acceptable salt thereof in a concentration of 0.2-5.0 (w/v)%, and an arylcarboxylic acid selected from the group consisting of pranoprofen, ibuprofen, bromfenac (2-amino-3-(4-bromobenzoyl)phenalyacetic acid), 2-naphthoic acid, 2-naphthylacetic acid and 2-naphthoxyacetic acid or a pharmacologically acceptable salt thereof in a proportion of 0.001-50 parts by weight per part by weight of the pyridonecarboxylic acid (see claim 2). The reference further teaches examples of the solubilizer include non-ionic surfactants such as polyoxyethylenesorbitane monoolate, polyoxyethyleneoxystearic acid triglyceride, polyethylene glycol, polyoxyethylene hydrogenated castor oil and the like, (col 8 lines 66-67 and col 9 lines 1-3). The aqueous solution of the present invention is used as an eye drop, nasal drop or ear drop. When it is used as an eye drop, its pH is generally adjusted to about 3.5-8.5, preferably about 6-8, when it is used as a nasal drop, its pH is generally adjusted to about 3.5-8.5, preferably about 6-8, (See claims 3-5). Examples of the antiseptic include quaternary ammonium salts such as benzalkonium chloride. Examples of the thickener include polyvinylpyrrolidone, Examples of the chelating agent include sodium edetate, pH adjusting agents include sodium hydroxide, the reference teaches boric acid.

Although, the reference teaches both 2-amino-3-(4-bromobenzoyl)phenalyacetic acid and a surfactant in an aqueous solution, the reference fails to specify an example and the specific elected species of the surfactant.

Chen et al. teaches 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. Chen et al. further teaches components that can be incorporated into the composition include inorganic acids inclusive of boric acid, solubilizer such as polyvinylpyrrolidone, exemplifications of carriers comprising Edetate Disodium, and ionizing agents that deprotonate the acidic functional groups of the therapeutic agent are pharmaceutically acceptable organic or inorganic bases, inclusive of sodium hydroxide (reads on the limitations of claim 22).

It would have been obvious to one of ordinary skill in the art to use a hydrophobic therapeutic agent, bromfenac, with the elected surfactant. The motivation comes from the teaching of Chen et al. that a variety of PEG-fatty acid esters have useful surfactant properties. Among the PEG-fatty acid monoesters, esters of lauric acid, oleic acid, and stearic acid are most useful. Hence, a skilled artisan would have reasonable expectation of successfully producing a composition with the most useful surfactant properties.

With respect to claim 19, the transitional phrase “consisting essentially of” limits the scope of a claim to the specified materials or steps “and those that do not materially affect the basic and novel characteristic(s)” of the claimed invention. In re Herz, 537 F.2d 549, 551-52, 190 USPQ 461, 463 (CCPA 1976). “A consisting essentially of' claim

occupies a middle ground between closed claims that are written in a consisting of' format and fully open claims that are drafted in a comprising' format." PPG Industries v. Guardian Industries, 156 F.3d 1351, 1354, 48 USPQ2d 1351, 1353-54 (Fed. Cir. 1998). See also Atlas Powder v. E.I. duPont de Nemours & Co., 750 F.2d 1569, 224 USPQ 409 (Fed. Cir. 1984); In re Janakirama-Rao, 317 F.2d 951, 137 USPQ 893 (CCPA 1963); Water Technologies Corp. vs. Calco, Ltd., 850 F.2d 660, 7 USPQ2d 1097 (Fed. Cir. 1988). For art purposes, "the consisting essentially of" language in the claim is treated as "comprising" language and it is an applicant's burden to establish that a step practiced in a prior art method is excluded from his claims by consisting essentially of' language." (See MPEP 2111.03)

Claims 1, 4-5, 8-9, 11-14, 19-22, and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sawa (6274592) in view of Chen et al. (US 6383471).

Sawa teaches an aqueous solution containing an arylcarboxylic acid or a pharmacologically acceptable salt thereof, particularly pranoprofen, dicrofenac or bromfenac(2-amino-3-(4-bromobenzoyl)phenalyacetic acid), and which has sufficient stability at lower temperatures. Examples of the solubilizer include non-ionic surfactants such as polyoxyethylenesorbitan monoolate, polyoxyethyleneoxystearic acid triglyceride, polyethylene glycol, polyoxyethylene hydrogenated castor oil and the like, (see col 11 lines 59-63). The aqueous solution of the present invention is used as an eye drop, nasal drop or ear drop. When it is used as an eye drop, its pH is generally adjusted to about 3.5-8.5, preferably about 6-8, when it is used as a nasal drop, its pH is generally adjusted to about 3.5-8.5, preferably about 6-8. Examples of the antiseptic

include quaternary ammonium salts such as benzalkonium chloride. Examples of the thickener include polyvinylpyrrolidone, Examples of the chelating agent include sodium edetate, pH adjusting agents include sodium hydroxide, the reference teaches boric acid.

Although, the reference teaches both 2-amino-3-(4-bromobenzoyl)phenalyacetic acid and a surfactant in an aqueous solution, the reference fails to specify an example and the specific elected species of the surfactant.

Chen et al. teaches 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. Chen et al. further teaches components that can be incorporated into the composition include inorganic acids inclusive of boric acid, solubilizer such as polyvinylpyrrolidone, exemplifications of carriers comprising Edetate Disodium, and ionizing agents that deprotonate the acidic functional groups of the therapeutic agent are pharmaceutically acceptable organic or inorganic bases, inclusive of sodium hydroxide (reads on the limitations of claim 22).

It would have been obvious to one of ordinary skill in the art to use a hydrophobic therapeutic agent, bromfenac, with the elected surfactant. The motivation comes from the teaching of Chen et al. that a variety of PEG-fatty acid esters have useful surfactant properties. Among the PEG-fatty acid monoesters, esters of lauric acid, oleic acid, and

stearic acid are most useful. Hence, a skilled artisan would have reasonable expectation of successfully producing a composition with the most useful surfactant properties.

With respect to claim 19, the transitional phrase “consisting essentially of” limits the scope of a claim to the specified materials or steps “and those that do not materially affect the basic and novel characteristic(s)” of the claimed invention. In re Herz, 537 F.2d 549, 551-52, 190 USPQ 461, 463 (CCPA 1976). “A consisting essentially of' claim occupies a middle ground between closed claims that are written in a consisting of' format and fully open claims that are drafted in a comprising' format.” PPG Industries v. Guardian Industries, 156 F.3d 1351, 1354, 48 USPQ2d 1351, 1353-54 (Fed. Cir. 1998). See also Atlas Powder v. E.I. duPont de Nemours & Co., 750 F.2d 1569, 224 USPQ 409 (Fed. Cir. 1984); In re Janakirama-Rao, 317 F.2d 951, 137 USPQ 893 (CCPA 1963); Water Technologies Corp. vs. Calco, Ltd., 850 F.2d 660, 7 USPQ2d 1097 (Fed. Cir. 1988). For art purposes, “the consisting essentially of” language in the claim is treated as “comprising” language and it is an applicant's burden to establish that a step practiced in a prior art method is excluded from his claims by consisting essentially of' language.” (See MPEP 2111.03)

Claims 1, 4-5, 8-9, 11-14, 19-22, and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sawa (20010056098) in view of Chen et al. (US 6383471).

Sawa teaches an aqueous solution which contains an arylcarboxylic acid or a pharmacologically acceptable salt thereof, particularly pranoprofen, dicrofenac or bromfenac (2-amino-3-(4-bromobenzoyl)phenalyacetic acid), and which has sufficient

stability at lower temperatures[0004]. Examples of the solubilizer include non-ionic surfactants such as polyoxyethylenesorbitan monoolate, polyoxyethyleneoxystearic acid triglyceride, polyethylene glycol, polyoxyethylene hydrogenated castor oil and the like, [0147]. The aqueous solution of the present invention is used as an eye drop, nasal drop or ear drop. When it is used as an eye drop, its pH is generally adjusted to about 3.5-8.5, preferably about 6-8, when it is used as a nasal drop, its pH is generally adjusted to about 3.5-8.5, preferably about 6-8. Examples of the antiseptic include quaternary ammonium salts such as benzalkonium chloride. Examples of the thickener include polyvinylpyrrolidone, Examples of the chelating agent include sodium edetate, pH adjusting agents include sodium hydroxide, the reference teaches boric acid.

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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. Chen et al. further teaches components that can be incorporated into the composition include inorganic acids inclusive of boric acid, solubilizer such as polyvinylpyrrolidone, exemplifications of carriers comprising Edetate Disodium, and ionizing agents that deprotonate the acidic functional groups of the therapeutic agent are pharmaceutically

acceptable organic or inorganic bases, inclusive of sodium hydroxide (reads on the limitations of claim 22).

It would have been obvious to one of ordinary skill in the art to use a hydrophobic therapeutic agent, bromfenac, with the elected surfactant. The motivation comes from the teaching of Chen et al. that a variety of PEG-fatty acid esters have useful surfactant properties. Among the PEG-fatty acid monoesters, esters of lauric acid, oleic acid, and stearic acid are most useful. Hence, a skilled artisan would have reasonable expectation of successfully producing a composition with the most useful surfactant properties.

With respect to claim 19, the transitional phrase “consisting essentially of” limits the scope of a claim to the specified materials or steps “and those that do not materially affect the basic and novel characteristic(s)” of the claimed invention. In re Herz, 537 F.2d 549, 551-52, 190 USPQ 461, 463 (CCPA 1976). “A consisting essentially of' claim occupies a middle ground between closed claims that are written in a consisting of' format and fully open claims that are drafted in a comprising' format.” PPG Industries v. Guardian Industries, 156 F.3d 1351, 1354, 48 USPQ2d 1351, 1353-54 (Fed. Cir. 1998). See also Atlas Powder v. E.I. duPont de Nemours & Co., 750 F.2d 1569, 224 USPQ 409 (Fed. Cir. 1984); In re Janakirama-Rao, 317 F.2d 951, 137 USPQ 893 (CCPA 1963); Water Technologies Corp. vs. Calco, Ltd., 850 F.2d 660, 7 USPQ2d 1097 (Fed. Cir. 1988). For art purposes, “the consisting essentially of” language in the claim is treated as “comprising” language and it is an applicant's burden to establish that a step

practiced in a prior art method is excluded from his claims by consisting essentially of' language." (See MPEP 2111.03)

Claim 7 is rejected under 35 U.S.C. 103(a) as being unpatentable over Chen et al. (US 6383471), as applied to claims 1, 4-5, 8, 19-20, 22, and 27 above, and further in view of Fukahori et al. (JP 402083323A).

Chen et al. is as discussed above.

Chen et al. fails to teach the specified amount of surfactant.

Fukahori et al. teaches a stable aqueous solution of riboflavin containing non-ionic surfactants preferably polyoxyethylene hardened castor oil or polyethylene glycol monostearate in an amount of 0.01 to 5.0 wt %/vol%.

In the absence of showing the criticality, the determination of optimal or workable concentration of the polyethylene glycol monostearate by routine experimentation is obvious absent showing of criticality of the claimed concentration. One having ordinary skill in the art would have been motivated to do this to obtain the desired stability and solubilizing properties of the composition. Hence, a skilled artisan would have had reasonable expectation of successfully producing a composition with the polyethylene glycol monostearate in the claimed range.

Claim 7 is rejected under 35 U.S.C. 103(a) as being unpatentable Sawa (5942508) in view of Chen et al. (US 6383471), as applied to claims 1, 4-5, 8-9, 11-14, 19-22, and 27 above, and further in view of Fukahori et al. (JP 402083323A).

Sawa and Chen et al. is as discussed above.

Sawa and Chen et al. fail to teach the specified amount of surfactant.

Fukahori et al. teaches a stable aqueous solution of riboflavin containing non-ionic surfactants preferably polyoxyethylene hardened castor oil or polyethylene glycol monostearate in an amount of 0.01 to 5.0 wt %/vol%.

In the absence of showing the criticality, the determination of optimal or workable concentration of the polyethylene glycol monostearate within the reference's generic disclosure by routine experimentation is obvious absent showing of criticality of the claimed concentration. One having ordinary skill in the art would have been motivated to do this to obtain the desired clarity of the composition. Hence, a skilled artisan would have had reasonable expectation of successfully producing a composition with the polyethylene glycol monostearate in the claimed range.

Claim 7 is rejected under 35 U.S.C. 103(a) as being unpatentable over Sawa (6274592) in view of Chen et al. (US 6383471), as applied to claims 1, 4-5, 8-9, 11-14, 19-22, and 27 above, and further in view of Fukahori et al. (JP 402083323A).

Sawa and Chen et al. is as discussed above.

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Claim 7 is rejected under 35 U.S.C. 103(a) as being unpatentable over Sawa (20010056098) in view of Chen et al. (US 6383471), as applied to claims 1, 4-5, 8, 13, 19-20, 22, and 27 above, and further in view of Fukahori et al. (JP 402083323A).

Sawa and Chen et al. is as discussed above.

Sawa and Chen et al. fail to teach the specified amount of surfactant.

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In the absence of showing the criticality, the determination of optimal or workable concentration of the polyethylene glycol monostearate within the reference's generic disclosure by routine experimentation is obvious absent showing of criticality of the claimed concentration. One having ordinary skill in the art would have been motivated to do this to obtain the desired clarity of the composition. Hence, a skilled artisan would

have had reasonable expectation of successfully producing a composition with the polyethylene glycol monostearate in the claimed range.

Claims 9, 11- 14, and 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chen et al. (US 6383471), as applied to claims 1, 4-5, 8, 19-20, 22, and 27 above, and further in view of Sawa (5942508).

Chen et al. is as discussed above.

Chen et al. fails to teach the pH range claimed, or that the ocular preparation is an eye drop, a nasal drop, and the preservative being a quaternary ammonium compound - benzalkonium chloride.

Sawa teaches an aqueous solution comprising a pyridonecarboxylic acid selected from the group consisting of lomefloxacin, norfloxacin, enoxacin, ofloxacin, ciprofloxacin, tosufloxacin, fleroxacin, cinoxacin, levofloxacin and sparfloxacin or a pharmacologically acceptable salt thereof in a concentration of 0.2-5.0 (w/v)%, and an arylcarboxylic acid selected from the group consisting of pranoprofen, ibuprofen, bromfenac, 2-naphthoic acid, 2-naphthylacetic acid and 2-naphthoxyacetic acid or a pharmacologically acceptable salt thereof in a proportion of 0.001-50 parts by weight per part by weight of the pyridonecarboxylic acid (see claim 2). The reference further teaches examples of the solubilizer include non-ionic surfactants such as polyoxyethylenesorbitane monoolate, polyoxyethyleneoxystearic acid triglyceride, polyethylene glycol, polyoxyethylene hydrogenated castor oil and the like, (col 8 lines

66-67 and col 9 lines 1-3). The aqueous solution of the present invention is used as an eye drop, nasal drop or ear drop. When it is used as an eye drop, its pH is generally adjusted to about 3.5-8.5, preferably about 6-8, when it is used as a nasal drop, its pH is generally adjusted to about 3.5-8.5, preferably about 6-8, (See claims 3-5). Examples of the antiseptic include quaternary ammonium salts such as benzalkonium chloride. Examples of the thickener include polyvinylpyrrolidone, Examples of the chelating agent include sodium edetate, pH adjusting agents include sodium hydroxide, the reference teaches boric acid.

It would have been obvious to one of ordinary skill in the art to use a preservative or specifically - benzalkonium chloride, making the pH range claimed, and an eye and nasal drop. The motivation comes from the teaching of Sawa that a an aqueous solution comprising bromfenac and non-ionic surfactants comprise benzalkonium chloride for its antiseptic properties; the formlation are present as eye drop, nasal drop or ear drop. When it is used as an eye drop, its pH is generally adjusted to about 3.5-8.5, preferably about 6-8, when it is used as a nasal drop, its pH is generally adjusted to about 3.5-8.5, preferably about 6-8. Hence, a skilled artisan would have reasonable expectation of successfully producing a composition with similar efficacy and results.

Claims 9, 11-14, and 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chen et al. (US 6383471), as applied to claims 1, 4-5, 8, 19-20, 22, and 27 above, and further in view of Sawa (6274592).

Chen et al. is as discussed above.

Chen et al. fails to teach the pH range claimed, or that the ocular preparation is an eye drop an eye drop, a nasal drop, and the perservative being a quaternary ammonium compound - benzalkonium chloride.

Sawa teaches an aqueous solution containing an arylcarboxylic acid or a pharmacologically acceptable salt thereof, particularly pranoprofen, dicrofenac or bromfenac, and which has sufficient stability at lower temperatures. Examples of the solubilizer include non-ionic surfactants such as polyoxyethylenesorbitan monoolate, polyoxyethyleneoxystearic acid triglyceride, polyethylene glycol, polyoxyethylene hydrogenated castor oil and the like, (see col 11 lines 59-63). The aqueous solution of the present invention is used as an eye drop, nasal drop or ear drop. When it is used as an eye drop, its pH is generally adjusted to about 3.5-8.5, preferably about 6-8, when it is used as a nasal drop, its pH is generally adjusted to about 3.5-8.5, preferably about 6-8. Examples of the antiseptic include quaternary ammonium salts such as benzalkonium chloride. Examples of the thickener include polyvinylpyrrolidone, Examples of the chelating agent include sodium edetate, pH adjusting agents include sodium hydroxide, the reference teaches boric acid.

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when it is used as a nasal drop, its pH is generally adjusted to about 3.5-8.5, preferably about 6-8. Hence, a skilled artisan would have reasonable expectation of successfully producing a composition with similar efficacy and results.

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Sawa teaches an aqueous solution which contains an arylcarboxylic acid or a pharmacologically acceptable salt thereof, particularly pranoprofen, dicrofenac or bromfenac, and which has sufficient stability at lower temperatures[0004]. Examples of the solubilizer include non-ionic surfactants such as polyoxyethylenesorbitan monoolate, polyoxyethyleneoxystearic acid triglyceride, polyethylene glycol, polyoxyethylene hydrogenated castor oil and the like, [0147]. The aqueous solution of the present invention is used as an eye drop, nasal drop or ear drop. When it is used as an eye drop, its pH is generally adjusted to about 3.5-8.5, preferably about 6-8, when it is used as a nasal drop, its pH is generally adjusted to about 3.5-8.5, preferably about 6-8. Examples of the antiseptic include quaternary ammonium salts such as benzalkonium chloride. Examples of the thickener include polyvinylpyrrolidone,

Examples of the chelating agent include sodium edetate, pH adjusting agents include sodium hydroxide, the reference teaches boric acid.

It would have been obvious to one of ordinary skill in the art to use a preservative or specifically - benzalkonium chloride, making the pH range claimed, and a nasal drop. The motivation comes from the teaching of Sawa that a an aqueous solution comprising bromfenac and non-ionic surfactants comprise benzalkonium chloride for its antiseptic properties; the formulation are present as eye drop, nasal drop or ear drop. When it is used as an eye drop, its pH is generally adjusted to about 3.5-8.5, preferably about 6-8, when it is used as a nasal drop, its pH is generally adjusted to about 3.5-8.5, preferably about 6-8. Hence, a skilled artisan would have reasonable expectation of successfully producing a composition with similar efficacy and results.

Claims 9, 21, and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chen et al. (US 6383471), as applied to claims 1, 4-5, 8, 19-20, 22, and 27 above, and further in view of Gamache et al. (WO 01/15677) and Yakuji Nippo Ltd., ("New Drugs in Japan: 2001", 2001 Edition, Published by May 11, 2001, p.27-29 - IDS).

Chen et al. is as discussed above.

Chen et al. fails to teach the specified preservative and stabilizer.

Gamache et al. teaches anti-inflammatory agents include bromfenac and Moxifloxacin, viscosity building agents include, for example, polyvinyl alcohol, polyvinyl pyrrolidone, methyl cellulose, hydroxypropyl methylcellulose, hydroxyethyl cellulose, carboxymethyl cellulose, hydroxypropyl cellulose or other agents known to those skilled

in the art. An appropriate buffer system (e. g., sodium phosphate, sodium acetate or sodium borate) may be added to prevent pH drift under storage conditions. Exemplified is an otic/nasal suspension: lngredient 1B/1 D agonist 0.1-1.0% w/v, Moxifloxacin 0.3% w/v, Benzalkonium Chloride 0.01% w/v, Edetate Disodium, USP 0.01% w/v, Sodium Chloride, USP 0.3% w/v, Sodium Sulfate, USP 1.2% w/v, Tyloxapol, USP 0.05% w/v, Hydroxyethylcellulose 0.25% w/v, Sulfuric Acid and/or Sodium Hydroxide, NF q. s., and purified water q. s. to 100%.

Yakuji Nippo Ltd. teaches an aqueous ophthalmic solution comprising bromfenac sodium hydrate boric acid, sodium sulfite, disodium edetate, polyvinylpyrroldione, benzalkonium sodium hydrate.

It would have been obvious to one of ordinary skill in the art at the time of the invention to use the specific preservative Benzalkonium Chloride and stabilizer - sodium sulfite. The motivation comes from the teaching of Gamache et al. that the preservatives inclusive of Benzalkonium Chloride prevent microbial contamination during use and the stabilizer prevent pH drift under storage conditions and further by Yakuji Nippo Ltd. that an ophthalmic solution of bromfenac sodium hydrate comprises boric acid, sodium sulfite, disodium edetate, polyvinylpyrroldione, benzalkonium sodium hydrate. Hence, a skilled artisan would have had reasonable expectation of successfully producing a composition with similar efficacy and results.

Claims 10, and 23-25 are rejected under 35 U.S.C. 103(a) as being unpatentable Sawa (5942508) in view of Chen et al. (US 6383471), as applied to claims 1, 4-5, 8-9, 11-14, 19-22, and 27 above, and further in view of Gamache et al. (WO

01/15677) and Yakuji Nippo Ltd., ("New Drugs in Japan: 2001", 2001 Edition, Published by May 11, 2001, p.27-29 - IDS).

Sawa and Chen et al. is as discussed above.

Sawa and Chen et al. fail to teach the specified sodium sulfite and the specified sodium salt or a hydrate.

Gamache et al. teaches anti-inflammatory agents include bromfenac and Moxifloxacin, viscosity building agents include, for example, polyvinyl alcohol, polyvinyl pyrrolidone, methyl cellulose, hydroxypropyl methylcellulose, hydroxyethyl cellulose, carboxymethyl cellulose, hydroxypropyl cellulose or other agents known to those skilled in the art. An appropriate buffer system (e. g., sodium phosphate, sodium acetate or sodium borate) may be added to prevent pH drift under storage conditions. Exemplified is an otic/nasal suspension: lngredient 1B/1 D agonist 0.1-1.0% w/v, Moxifloxacin 0.3% w/v, Benzalkonium Chloride 0.01% w/v, Edetate Disodium, USP 0.01% w/v, Sodium Chloride, USP 0.3% w/v, Sodium Sulfate, USP 1.2% w/v, Tyloxapol, USP 0.05% w/v, Hydroxyethylcellulose 0.25% w/v, Sulfuric Acid and/or Sodium Hydroxide, NF q. s., and purified water q. s. to 100%.

Yakuji Nippo Ltd. teaches an aqueous ophthalmic solution comprising bromfenac sodium hydrate boric acid, sodium sulfite, disodium edetate, polyvinylpyrroldione, benzalkonium sodium hydrate.

It would have been obvious to one of ordinary skill in the art at the time of the invention to use the specific stabilizer - sodium sulfite. The motivation comes from the

teaching of Gamache et al. that the stabilizer prevents pH drift under storage conditions and further by Yakuji Nippo Ltd. that an ophthalmic solution of bromfenac sodium hydrate comprises boric acid, sodium sulfite, disodium edetate, polyvinylpyrroldione, benzalkonium sodium hydrate. Hence, a skilled artisan would have had reasonable expectation of successfully producing a composition with similar efficacy and results.

Claims 10, and 23-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sawa (6274592) in view of Chen et al. (US 6383471), as applied to claims 1, 4-5, 8-9, 11-14, 19-22, and 27 above, and further in view of Gamache et al. (WO 01/15677) and Yakuji Nippo Ltd., ("New Drugs in Japan: 2001", 2001 Edition, Published by May 11, 2001, p.27-29 - IDS).

Sawa and Chen et al. is as discussed above.

Sawa and Chen et al. fail to teach the specified sodium sulfite.

Gamache et al. teaches anti-inflammatory agents include bromfenac and Moxifloxacin, viscosity building agents include, for example, polyvinyl alcohol, polyvinyl pyrrolidone, methyl cellulose, hydroxypropyl methylcellulose, hydroxyethyl cellulose, carboxymethyl cellulose, hydroxypropyl cellulose or other agents known to those skilled in the art. An appropriate buffer system (e. g., sodium phosphate, sodium acetate or sodium borate) may be added to prevent pH drift under storage conditions. Exemplified is an otic/nasal suspension: Ingredient 1B/1 D agonist 0.1-1.0% w/v, Moxifloxacin 0.3% w/v, Benzalkonium Chloride 0.01% w/v, Edetate Disodium, USP 0.01% w/v, Sodium Chloride, USP 0.3% w/v, Sodium Sulfate, USP 1.2% w/v, Tyloxapol, USP 0.05% w/v,

Hydroxyethylcellulose 0.25% w/v, Sulfuric Acid and/or Sodium Hydroxide, NF q. s., and purified water q. s. to 100%.

Yakuji Nippo Ltd. teaches an aqueous ophthalmic solution comprising bromfenac sodium hydrate boric acid, sodium sulfite, disodium edetate, polyvinylpyrroldione, benzalkonium sodium hydrate.

It would have been obvious to one of ordinary skill in the art at the time of the invention to use the specific stabilizer - sodium sulfite. The motivation comes from the teaching of Gamache et al. that the stabilizer prevents pH drift under storage conditions and further by Yakuji Nippo Ltd. that an ophthalmic solution of bromfenac sodium hydrate comprises boric acid, sodium sulfite, disodium edetate, polyvinylpyrroldione, benzalkonium sodium hydrate. Hence, a skilled artisan would have had reasonable expectation of successfully producing a composition with similar efficacy and results.

Claims 10, and 23-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sawa (20010056098) in view of Chen et al. (US 6383471), as applied to claims 1, 4-5, 8, 13, 19-20, 22, 24, and 27 above, and further in view of Gamache et al. (WO 01/15677) and Yakuji Nippo Ltd., ("New Drugs in Japan: 2001", 2001 Edition, Published by May 11, 2001, p.27-29 - IDS).

Sawa and Chen et al. is as discussed above.

Sawa and Chen et al. fail to teach the specified sodium sulfite.

Gamache et al. teaches anti-inflammatory agents include bromfenac and Moxifloxacin, viscosity building agents include, for example, polyvinyl alcohol, polyvinyl

pyrrolidone, methyl cellulose, hydroxypropyl methylcellulose, hydroxyethyl cellulose, carboxymethyl cellulose, hydroxypropyl cellulose or other agents known to those skilled in the art. An appropriate buffer system (e. g., sodium phosphate, sodium acetate or sodium borate) may be added to prevent pH drift under storage conditions. Exemplified is an otic/nasal suspension: lngredient 1B/1 D agonist 0.1-1.0% w/v, Moxifloxacin 0.3% w/v, Benzalkonium Chloride 0.01% w/v, Edetate Disodium, USP 0.01% w/v, Sodium Chloride, USP 0.3% w/v, Sodium Sulfate, USP 1.2% w/v, Tyloxapol, USP 0.05% w/v, Hydroxyethylcellulose 0.25% w/v, Sulfuric Acid and/or Sodium Hydroxide, NF q. s., and purified water q. s. to 100%.

Yakuji Nippo Ltd. teaches an aqueous ophthalmic solution comprising bromfenac sodium hydrate boric acid, sodium sulfite, disodium edetate, polyvinylpyrroldione, benzalkonium sodium hydrate.

It would have been obvious to one of ordinary skill in the art at the time of the invention to use the specific stabilizer - sodium sulfite. The motivation comes from the teaching of Gamache et al. that the stabilizer prevents pH drift under storage conditions and further by Yakuji Nippo Ltd. that an ophthalmic solution of bromfenac sodium hydrate comprises boric acid, sodium sulfite, disodium edetate, polyvinylpyrroldione, benzalkonium sodium hydrate. Hence, a skilled artisan would have had reasonable expectation of successfully producing a composition with similar efficacy and results.

Claim 16 is rejected under 35 U.S.C. 103(a) as being unpatentable over Chen et al. (US 6383471) and Fukahori et al. (JP 402083323A), as applied to claims 1, 4-5, 7-8, 19-20, 22, and 27 above, and further in view of Aikawa et al. (JP 2002308764 A).

Chen et al. and Fukahori et al. are as discussed above.

Chen et al. and Fukahori et al. fail to teach the specified sodium salt or a hydrate.

Aikawa et al. teaches ophthalmic pharmaceutical composition (eye drop) for treating or preventing congestion symptom of a conjunctiva, contains bromfenac sodium hydrate.

It would have been obvious to one of ordinary skill in the art to use the sodium salt and hydrate of bromfenac. The motivation comes from the teaching of Aikawa et al. that an aqueous solution (eye drop) comprising bromfenac sodium hydrate treats or prevents congestion symptom of a conjunctiva. Hence, a skilled artisan would have reasonable expectation of successfully producing a composition with similar efficacy and results.

Claim 16 is rejected under 35 U.S.C. 103(a) as being unpatentable Sawa (5942508) in view of Chen et al. (US 6383471) and Fukahori et al. (JP 402083323A), as applied to claims 1, 4-5, 7-9, 11-14, 19-22, and 27 above, and further in view of Aikawa et al. (JP 2002308764 A).

Sawa, Chen et al. and Fukahori et al. are as discussed above.

Sawa, Chen et al. and Fukahori et al. fail to teach the specified sodium salt or a hydrate.

Aikawa et al. teaches ophthalmic pharmaceutical composition (eye drop) for treating or preventing congestion symptom of a conjunctiva, contains bromfenac sodium hydrate.

It would have been obvious to one of ordinary skill in the art to use the sodium salt and hydrate of bromfenac. The motivation comes from the teaching of Aikawa et al. that an aqueous solution (eye drop) comprising bromfenac sodium hydrate treats or prevents congestion symptom of a conjunctiva. Hence, a skilled artisan would have reasonable expectation of successfully producing a composition with similar efficacy and results.

Claim 16 is rejected under 35 U.S.C. 103(a) as being unpatentable over Sawa (6274592) in view of Chen et al. (US 6383471) and Fukahori et al. (JP 402083323A), as applied to claims 1, 4-5, 7-9, 11-14, 19-22, and 27 above, and further in view of Aikawa et al. (JP 2002308764 A).

Sawa, Chen et al. and Fukahori et al. is as discussed above.

Sawa, Chen et al. and Fukahori et al. fail to teach the specified sodium salt or a hydrate.

Aikawa et al. teaches ophthalmic pharmaceutical composition (eye drop) for treating or preventing congestion symptom of a conjunctiva, contains bromfenac sodium hydrate.

It would have been obvious to one of ordinary skill in the art to use the sodium salt and hydrate of bromfenac. The motivation comes from the teaching of Aikawa et al. that an aqueous solution (eye drop) comprising bromfenac sodium hydrate treats or prevents congestion symptom of a conjunctiva. Hence, a skilled artisan would have reasonable expectation of successfully producing a composition with similar efficacy and results.

Claim 16 is rejected under 35 U.S.C. 103(a) as being unpatentable over Sawa (20010056098) in view of Chen et al. (US 6383471) and Fukahori et al. (JP 402083323A), as applied to claims 1, 4-5, 7-8, 13, 19-20, 22, and 27 above, and further in view of Aikawa et al. (JP 2002308764 A).

Sawa, Chen et al. and Fukahori et al. is as discussed above.

Sawa, Chen et al. and Fukahori et al. fail to teach the specified sodium salt or a hydrate.

Aikawa et al. teaches ophthalmic pharmaceutical composition (eye drop) for treating or preventing congestion symptom of a conjunctiva, contains bromfenac sodium hydrate.

It would have been obvious to one of ordinary skill in the art to use the sodium salt and hydrate of bromfenac. The motivation comes from the teaching of Aikawa et al. that an aqueous solution (eye drop) comprising bromfenac sodium hydrate treats or prevents congestion symptom of a conjunctiva. Hence, a skilled artisan would have

reasonable expectation of successfully producing a composition with similar efficacy and results.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 4-5, 8, 11-14, 19-20, 22, and 27 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-3 and 5-6 of U.S. Patent No. 7829544 in view of Chen et al. (US 6383471). Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims are drawn to an aqueous solution preparation according to claim 1, wherein the concentration of the aminoglycoside antibiotic or its pharmacologically acceptable salt in the aqueous solution preparation is within a range from a minimum of 0.01 w/v % to a maximum of 35.0 w/v %, and the concentration of the bromfenac or its pharmacologically acceptable salt in the aqueous solution preparation is within a range from a minimum of 0.01 w/v % to a maximum of 0.5 w/v %; further comprising at least one compound selected from the group consisting of a nonionic water-soluble polymer and a nonionic surfactant whereas the claims herein are drawn to an aqueous liquid preparation comprising 2-amino-3-(4- bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof, and an alkyl aryl polyether alcohol type polymer or a polyethylene glycol fatty acid ester.

Although, the reference teaches both 2-amino-3-(4-bromobenzoyl)phenalyacetic acid and a surfactant in an aqueous solution, the reference fails to specify an example and the specific elected species of the surfactant.

Chen et al. teaches 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. Chen et al. further teaches components that can be incorporated into the composition include inorganic acids inclusive of boric acid, solubilizer such as polyvinylpyrrolidone, exemplifications of carriers comprising Edetate Disodium, and ionizing agents that deprotonate the acidic functional groups of the therapeutic agent are pharmaceutically acceptable organic or inorganic bases, inclusive of sodium hydroxide (reads on the limitations of claim 22).

It would have been obvious to one of ordinary skill in the art to use a hydrophobic therapeutic agent, bromfenac, with the elected surfactant. The motivation comes from the teaching of Chen et al. that a variety of PEG-fatty acid esters have useful surfactant properties. Among the PEG-fatty acid monoesters, esters of lauric acid, oleic acid, and stearic acid are most useful. Hence, a skilled artisan would have reasonable expectation of successfully producing a composition with the most useful surfactant properties.

With respect to claim 19, the transitional phrase “consisting essentially of” limits the scope of a claim to the specified materials or steps “and those that do not materially affect the basic and novel characteristic(s)” of the claimed invention. In re Herz, 537 F.2d 549, 551-52, 190 USPQ 461, 463 (CCPA 1976). “A consisting essentially of' claim

occupies a middle ground between closed claims that are written in a consisting of' format and fully open claims that are drafted in a comprising' format." PPG Industries v. Guardian Industries, 156 F.3d 1351, 1354, 48 USPQ2d 1351, 1353-54 (Fed. Cir. 1998). See also Atlas Powder v. E.I. duPont de Nemours & Co., 750 F.2d 1569, 224 USPQ 409 (Fed. Cir. 1984); In re Janakirama-Rao, 317 F.2d 951, 137 USPQ 893 (CCPA 1963); Water Technologies Corp. vs. Calco, Ltd., 850 F.2d 660, 7 USPQ2d 1097 (Fed. Cir. 1988). For art purposes, "the consisting essentially of" language in the claim is treated as "comprising" language and it is an applicant's burden to establish that a step practiced in a prior art method is excluded from his claims by consisting essentially of' language." (See MPEP 2111.03)

Claim 7 is rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-3 and 5-6 of U.S. Patent No. 7829544 in view of Chen et al. (US 6383471), as applied to claims 1, 4-5, 8, 11-14, 19-20, 22, and 27 above and further in view of Fukahori et al. (JP 402083323A). Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims are drawn to an aqueous solution preparation according to claim 1, wherein the concentration of the aminoglycoside antibiotic or its pharmacologically acceptable salt in the aqueous solution preparation is within a range from a minimum of 0.01 w/v % to a maximum of 35.0 w/v %, and the concentration of the bromfenac or its pharmacologically acceptable salt in the aqueous solution preparation is within a range from a minimum of 0.01 w/v % to a maximum of 0.5 w/v %; further comprising at least one compound selected from the group consisting of a nonionic water-soluble polymer

and a nonionic surfactant whereas the claims herein are drawn to an aqueous liquid preparation comprising 2-amino-3-(4- bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof, and an alkyl aryl polyether alcohol type polymer or a polyethylene glycol fatty acid ester.

U.S. Patent No. 7829544 and Chen et al. (US 6383471) are discussed above.

U.S. Patent No. 7829544 and Chen et al. (US 6383471) fail to teach the amount of the polyethylene glycol as claimed.

Fukahori et al. teaches a stable aqueous solution of riboflavin containing non-ionic surfactants preferably polyoxyethylene hardened castor oil or polyethylene glycol monostearate in an amount of 0.01 to 5.0 wt %/vol%.

In the absence of showing the criticality, the determination of optimal or workable concentration of the polyethylene glycol monostearate by routine experimentation is obvious absent showing of criticality of the claimed concentration. One having ordinary skill in the art would have been motivated to do this to obtain the **desired stability and solubilizing** properties of the composition. Hence, a skilled artisan would have had reasonable expectation of successfully producing a composition with the polyethylene glycol monostearate in the claimed range.

Claims 9-10, 21, and 23-25 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-3 and 5-6 of U.S. Patent No. 7829544 in view of Chen et al. (US 6383471), as applied to claims 1, 4-5, 8, 11-14, 19-20, 22, and 27 above and further in view of Gamache et al. (WO

01/15677) and Yakuji Nippo Ltd., ("New Drugs in Japan: 2001", 2001 Edition, Published by May 11, 2001, p.27-29 - IDS). Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims are drawn to an aqueous solution preparation according to claim 1, wherein the concentration of the aminoglycoside antibiotic or its pharmacologically acceptable salt in the aqueous solution preparation is within a range from a minimum of 0.01 w/v % to a maximum of 35.0 w/v %, and the concentration of the bromfenac or its pharmacologically acceptable salt in the aqueous solution preparation is within a range from a minimum of 0.01 w/v % to a maximum of 0.5 w/v %; further comprising at least one compound selected from the group consisting of a nonionic water-soluble polymer and a nonionic surfactant whereas the claims herein are drawn to an aqueous liquid preparation comprising 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof, and an alkyl aryl polyether alcohol type polymer or a polyethylene glycol fatty acid ester.

U.S. Patent No. 7829544 and Chen et al. (US 6383471) are discussed above.

U.S. Patent No. 7829544 and Chen et al. (US 6383471) fail to teach the specified preservative and stabilizer; or salt and hydrate.

Gamache et al. teaches anti-inflammatory agents include bromfenac and Moxifloxacin, viscosity building agents include, for example, polyvinyl alcohol, polyvinyl pyrrolidone, methyl cellulose, hydroxypropyl methylcellulose, hydroxyethyl cellulose, carboxymethyl cellulose, hydroxypropyl cellulose or other agents known to those skilled in the art. An appropriate buffer system (e. g., sodium phosphate, sodium acetate or

sodium borate) may be added to prevent pH drift under storage conditions. Exemplified is an otic/nasal suspension: Ingredient 1B/1 D agonist 0.1-1.0% w/v, Moxifloxacin 0.3% w/v, Benzalkonium Chloride 0.01% w/v, Edetate Disodium, USP 0.01% w/v, Sodium Chloride, USP 0.3% w/v, Sodium Sulfate, USP 1.2% w/v, Tyloxapol, USP 0.05% w/v, Hydroxyethylcellulose 0.25% w/v, Sulfuric Acid and/or Sodium Hydroxide, NF q. s., and purified water q. s. to 100%.

Yakuji Nippo Ltd. teaches an aqueous ophthalmic solution comprising bromfenac sodium hydrate boric acid, sodium sulfite, disodium edetate, polyvinylpyrroldione, benzalkonium sodium hydrate.

It would have been obvious to one of ordinary skill in the art at the time of the invention to use the specific preservative Benzalkonium Chloride and stabilizer - sodium sulfite. The motivation comes from the teaching of Gamache et al. that the preservatives inclusive of Benzalkonium Chloride prevent microbial contamination during use and the stabilizer prevent pH drift under storage conditions and further by Yakuji Nippo Ltd. that an ophthalmic solution of bromfenac sodium hydrate comprises boric acid, sodium sulfite, disodium edetate, polyvinylpyrroldione, benzalkonium sodium hydrate. Hence, a skilled artisan would have had reasonable expectation of successfully producing a composition with similar efficacy and results.

Claim 16 is rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-3 and 5-6 of U.S. Patent No. 7829544 in view of Chen et al. (US 6383471) and Fukahori et al. (JP 402083323A), as applied to claims 1, 4-5, 7-8, 11-14, 19-20, 22, and 27 above and further in view of Aikawa et al.

(JP 2002308764 A). Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims are drawn to an aqueous solution preparation according to claim 1, wherein the concentration of the aminoglycoside antibiotic or its pharmacologically acceptable salt in the aqueous solution preparation is within a range from a minimum of 0.01 w/v % to a maximum of 35.0 w/v %, and the concentration of the bromfenac or its pharmacologically acceptable salt in the aqueous solution preparation is within a range from a minimum of 0.01 w/v % to a maximum of 0.5 w/v %; further comprising at least one compound selected from the group consisting of a nonionic water-soluble polymer and a nonionic surfactant whereas the claims herein are drawn to an aqueous liquid preparation comprising 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof, and an alkyl aryl polyether alcohol type polymer or a polyethylene glycol fatty acid ester.

U.S. Patent No. 7829544 and Chen et al. (US 6383471) are discussed above.

U.S. Patent No. 7829544 and Chen et al. (US 6383471) fail to teach the amount of the polyethylene glycol as claimed.

Chen et al. and Fukahori et al. are as discussed above.

Chen et al. and Fukahori et al. fail to teach the specified sodium salt or a hydrate.

Aikawa et al. teaches ophthalmic pharmaceutical composition (eye drop) for treating or preventing congestion symptom of a conjunctiva, contains bromfenac sodium hydrate.

It would have been obvious to one of ordinary skill in the art to use the sodium salt and hydrate of bromfenac. The motivation comes from the teaching of Aikawa et al. that an aqueous solution (eye drop) comprising bromfenac sodium hydrate treats or prevents congestion symptom of a conjunctiva. Hence, a skilled artisan would have reasonable expectation of successfully producing a composition with similar efficacy and results.

Claims 1, 4-5, 8, 13-14, 19-20, 22, and 27 rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-5 of U.S. Patent No. 5942508 in view of Chen et al. (US 6383471). Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims are drawn to an aqueous solution comprising a pyridonecarboxylic acid selected from the group consisting of lomefloxacin, norfloxacin, enoxacin, ofloxacin, ciprofloxacin, tosufloxacin, fleroxacin, cinoxacin, levofloxacin and sparfloxacin or a pharmacologically acceptable salt thereof in a concentration of 0.2-5.0 (w/v)%, and an arylcarboxylic acid selected from the group consisting of pranoprofen, ibuprofen, bromfenac, 2-naphthoic acid, 2-naphthylacetic acid and 2-naphthoxyacetic acid or a pharmacologically acceptable salt thereof in a proportion of 0.001-50 parts by weight per part by weight of the pyridonecarboxylic acid whereas the claims herein are drawn to an aqueous liquid preparation comprising 2-amino-3-(4- bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof, and an alkyl aryl polyether alcohol type polymer or a polyethylene glycol fatty acid ester.

Although, the reference teaches 2-amino-3-(4-bromobenzoyl)phenalyacetic acid in an eye and nasal drop the reference fails to specify an example and the specific elected species of the surfactant.

Chen et al. teaches 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). 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). 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

It would have been obvious to one of ordinary skill in the art to use a hydrophobic therapeutic agent, bromfenac, with the elected surfactant. The motivation comes from the teaching of Chen et al. that a variety of PEG-fatty acid esters have useful surfactant properties. Among the PEG-fatty acid monoesters, esters of lauric acid, oleic acid, and stearic acid are most useful. Hence, a skilled artisan would have reasonable expectation of successfully producing a composition with the most useful surfactant properties.

With respect to claim 19, the transitional phrase “consisting essentially of” limits the scope of a claim to the specified materials or steps “and those that do not materially affect the basic and novel characteristic(s)” of the claimed invention. In re Herz, 537 F.2d 549, 551-52, 190 USPQ 461, 463 (CCPA 1976). “A consisting essentially of' claim occupies a middle ground between closed claims that are written in a consisting of' format and fully open claims that are drafted in a comprising' format.” PPG Industries v. Guardian Industries, 156 F.3d 1351, 1354, 48 USPQ2d 1351, 1353-54 (Fed. Cir. 1998). See also Atlas Powder v. E.I. duPont de Nemours & Co., 750 F.2d 1569, 224 USPQ

409 (Fed. Cir. 1984); In re Janakirama-Rao, 317 F.2d 951, 137 USPQ 893 (CCPA 1963); Water Technologies Corp. vs. Calco, Ltd., 850 F.2d 660, 7 USPQ2d 1097 (Fed. Cir. 1988). For art purposes, “the consisting essentially of” language in the claim is treated as “comprising” language and it is an applicant's burden to establish that a step practiced in a prior art method is excluded from his claims by consisting essentially of' language.” (See MPEP 2111.03)

Claim 7 is rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-5 of U.S. Patent No. 5942508 in view of Chen et al. (US 6383471), as applied to claims 1, 4-5, 8, 13-14, 19-20, 22, and 27 above and further in view of Fukahori et al. (JP 402083323A). Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims are drawn to an aqueous solution comprising a pyridonecarboxylic acid selected from the group consisting of lomefloxacin, norfloxacin, enoxacin, ofloxacin, ciprofloxacin, tosufloxacin, fleroxacin, cinoxacin, levofloxacin and sparfloxacin or a pharmacologically acceptable salt thereof in a concentration of 0.2-5.0 (w/v)%, and an arylcarboxylic acid selected from the group consisting of pranoprofen, ibuprofen, bromfenac, 2-naphthoic acid, 2-naphthylacetic acid and 2-naphthoxyacetic acid or a pharmacologically acceptable salt thereof in a proportion of 0.001-50 parts by weight per part by weight of the pyridonecarboxylic acid whereas the claims herein are drawn to an aqueous liquid preparation comprising 2-amino-3-(4- bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof, and an alkyl aryl polyether alcohol type polymer or a polyethylene glycol fatty acid ester.

U.S. Patent No. 5942508 and Chen et al. (US 6383471) are discussed above.

U.S. Patent No. 5942508 and Chen et al. (US 6383471) fail to teach the amount of the polyethylene glycol as claimed.

Fukahori et al. teaches a stable aqueous solution of riboflavin containing non-ionic surfactants preferably polyoxyethylene hardened castor oil or polyethylene glycol monostearate in an amount of 0.01 to 5.0 wt %/vol%.

In the absence of showing the criticality, the determination of optimal or workable concentration of the polyethylene glycol monostearate by routine experimentation is obvious absent showing of criticality of the claimed concentration. One having ordinary skill in the art would have been motivated to do this to obtain the **desired stability and solubilizing** properties of the composition. Hence, a skilled artisan would have had reasonable expectation of successfully producing a composition with the polyethylene glycol monostearate in the claimed range.

Claims 9-10, 21, and 23-25 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-3 and 5-6 of U.S. Patent No. 5942508 in view of Chen et al. (US 6383471), as applied to claims 1, 4-5, 8, 13-14, 19-20, 22, and 27 above and further in view of Gamache et al. (WO 01/15677) and Yakuji Nippo Ltd., ("New Drugs in Japan: 2001", 2001 Edition, Published by May 11, 2001, p.27-29 - IDS). Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims are drawn to an aqueous solution comprising a pyridonecarboxylic acid selected from the group consisting of lomefloxacin, norfloxacin, enoxacin, ofloxacin, ciprofloxacin, tosufloxacin, fleroxacin,

cinoxacin, levofloxacin and sparfloxacin or a pharmacologically acceptable salt thereof in a concentration of 0.2-5.0 (w/v)%, and an arylcarboxylic acid selected from the group consisting of pranoprofen, ibuprofen, bromfenac, 2-naphthoic acid, 2-naphthylacetic acid and 2-naphthoxyacetic acid or a pharmacologically acceptable salt thereof in a proportion of 0.001-50 parts by weight per part by weight of the pyridonecarboxylic acid whereas the claims herein are drawn to an aqueous liquid preparation comprising 2-amino-3-(4- bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof, and an alkyl aryl polyether alcohol type polymer or a polyethylene glycol fatty acid ester.

U.S. Patent No. 5942508 and Chen et al. (US 6383471) are discussed above.

U.S. Patent No. 5942508 and Chen et al. (US 6383471) fail to teach the specified preservative and stabilizer; or salt and hydrate.

Gamache et al. teaches anti-inflammatory agents include bromfenac and Moxifloxacin, viscosity building agents include, for example, polyvinyl alcohol, polyvinyl pyrrolidone, methyl cellulose, hydroxypropyl methylcellulose, hydroxyethyl cellulose, carboxymethyl cellulose, hydroxypropyl cellulose or other agents known to those skilled in the art. An appropriate buffer system (e. g., sodium phosphate, sodium acetate or sodium borate) may be added to prevent pH drift under storage conditions. Exemplified is an otic/nasal suspension: lngredient 1B/1 D agonist 0.1-1.0% w/v, Moxifloxacin 0.3% w/v, Benzalkonium Chloride 0.01% w/v, Edetate Disodium, USP 0.01% w/v, Sodium Chloride, USP 0.3% w/v, Sodium Sulfate, USP 1.2% w/v, Tyloxapol, USP 0.05% w/v,

Hydroxyethylcellulose 0.25% w/v, Sulfuric Acid and/or Sodium Hydroxide, NF q. s., and purified water q. s. to 100%.

Yakuji Nippo Ltd. teaches an aqueous ophthalmic solution comprising bromfenac sodium hydrate boric acid, sodium sulfite, disodium edetate, polyvinylpyrroldione, benzalkonium sodium hydrate.

It would have been obvious to one of ordinary skill in the art at the time of the invention to use the specific preservative Benzalkonium Chloride and stabilizer - sodium sulfite. The motivation comes from the teaching of Gamache et al. that the preservatives inclusive of Benzalkonium Chloride prevent microbial contamination during use and the stabilizer prevent pH drift under storage conditions and further by Yakuji Nippo Ltd. that an ophthalmic solution of bromfenac sodium hydrate comprises boric acid, sodium sulfite, disodium edetate, polyvinylpyrroldione, benzalkonium sodium hydrate. Hence, a skilled artisan would have had reasonable expectation of successfully producing a composition with similar efficacy and results.

Claims 11 and 12 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-3 and 5-6 of U.S. Patent No. 5942508 in view of Chen et al. (US 6383471), as applied to claims 1, 4-5, 8, 11-14, 19-20, 22, and 27 above and further in view of Sawa (20010056098). Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims are drawn to an aqueous solution comprising a pyridonecarboxylic acid selected from the group consisting of lomefloxacin, norfloxacin, enoxacin, ofloxacin, ciprofloxacin, tosufloxacin, fleroxacin, cinoxacin, levofloxacin and sparfloxacin

or a pharmacologically acceptable salt thereof in a concentration of 0.2-5.0 (w/v)%, and an arylcarboxylic acid selected from the group consisting of pranoprofen, ibuprofen, bromfenac, 2-naphthoic acid, 2-naphthylacetic acid and 2-naphthoxyacetic acid or a pharmacologically acceptable salt thereof in a proportion of 0.001-50 parts by weight per part by weight of the pyridonecarboxylic acid whereas the claims herein are drawn to an aqueous liquid preparation comprising 2-amino-3-(4- bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof, and an alkyl aryl polyether alcohol type polymer or a polyethylene glycol fatty acid ester.

U.S. Patent No. 5942508 and Chen et al. (US 6383471) are discussed above.

U.S. Patent No. 5942508 and Chen et al. (US 6383471) fails to teach the pH range claimed.

Sawa teaches an aqueous solution which contains an arylcarboxylic acid or a pharmacologically acceptable salt thereof, particularly pranoprofen, dicrofenac or bromfenac, and which has sufficient stability at lower temperatures[0004]. Examples of the solubilizer include non-ionic surfactants such as polyoxyethylenesorbitan monoolate, polyoxyethyleneoxystearic acid triglyceride, polyethylene glycol, polyoxyethylene hydrogenated castor oil and the like, [0147]. The aqueous solution of the present invention is used as an eye drop, nasal drop or ear drop. When it is used as an eye drop, its pH is generally adjusted to about 3.5-8.5, preferably about 6-8, when it is used as a nasal drop, its pH is generally adjusted to about 3.5-8.5, preferably about 6-8. Examples of the antiseptic include quaternary ammonium salts such as benzalkonium chloride. Examples of the thickener include polyvinylpyrrolidone,

Examples of the chelating agent include sodium edetate, pH adjusting agents include sodium hydroxide, the reference teaches boric acid.

It would have been obvious to one of ordinary skill in the art to use a preservative or specifically - benzalkonium chloride, making the pH range claimed, and a nasal drop. The motivation comes from the teaching of Sawa that a an aqueous solution comprising bromfenac and non-ionic surfactants comprise benzalkonium chloride for its antiseptic properties; the formlation are present as eye drop, nasal drop or ear drop. When it is used as an eye drop, its pH is generally adjusted to about 3.5-8.5, preferably about 6-8, when it is used as a nasal drop, its pH is generally adjusted to about 3.5-8.5, preferably about 6-8. Hence, a skilled artisan would have reasonable expectation of successfully producing a composition with similar efficacy and results.

Claim 16 is rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-3 and 5-6 of U.S. Patent No. 5942508 in view of Chen et al. (US 6383471) and Fukahori et al. (JP 402083323A), as applied to claims 1, 4-5, 7-8, 13-14, 19-20, 22, and 27 above and further in view of Aikawa et al. (JP 2002308764 A). Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims are drawn to an aqueous solution preparation according to claim 1, wherein the concentration of the aminoglycoside antibiotic or its pharmacologically acceptable salt in the aqueous solution preparation is within a range from a minimum of 0.01 w/v % to a maximum of 35.0 w/v %, and the concentration of the bromfenac or its pharmacologically acceptable salt in the aqueous solution preparation is within a range from a minimum of 0.01 w/v %

to a maximum of 0.5 w/v %; further comprising at least one compound selected from the group consisting of a nonionic water-soluble polymer and a nonionic surfactant whereas the claims herein are drawn to an aqueous liquid preparation comprising 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof, and an alkyl aryl polyether alcohol type polymer or a polyethylene glycol fatty acid ester.

U.S. Patent No. 5942508, Chen et al. (US 6383471), and Fukahori et al. (JP 402083323A) are discussed above.

U.S. Patent No. 5942508 and Chen et al. (US 6383471), and Fukahori et al. (JP 402083323A) fail to teach the specified sodium salt or a hydrate.

Aikawa et al. teaches ophthalmic pharmaceutical composition (eye drop) for treating or preventing congestion symptom of a conjunctiva, contains bromfenac sodium hydrate.

It would have been obvious to one of ordinary skill in the art to use the sodium salt and hydrate of bromfenac. The motivation comes from the teaching of Aikawa et al. that an aqueous solution (eye drop) comprising bromfenac sodium hydrate treats or prevents congestion symptom of a conjunctiva. Hence, a skilled artisan would have reasonable expectation of successfully producing a composition with similar efficacy and results.

Claims 1, 4-5, 8, 10-12, 19-20, 22, and 27 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over

claims 1, 5, and 47-48 of copending Application No. 11755662 in view of Chen et al. (US 6383471). Although the conflicting claims are not identical, they are not patentably distinct from each other because the copending application is drawn to a method of treating pain and/or inflammation associated with an ocular disease, injury or disorder comprising administering to a patient, in need of such treatment, a stabilized aqueous liquid solution comprising 2-amino-3-(4-bromobenzoyl) phenylacetic acid or a pharmaceutically acceptable salt thereof or a hydrate thereof at a concentration ranging from 0.05% to 0.1% administered once or twice a day, or at a concentration ranging from 0.12% to 0.24% administered once a day, and an alkyl aryl polyether alcohol type polymer whereas the claims herein are drawn to an aqueous liquid preparation comprising 2-amino-3-(4- bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof, and an alkyl aryl polyether alcohol type polymer or a polyethylene glycol fatty acid ester.

Although, the reference teaches 2-amino-3-(4-bromobenzoyl)phenalyacetic acid and a carrier the reference fails to specify an example and the specific elected species of the surfactant.

Chen et al. teaches 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). 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). 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

It would have been obvious to one of ordinary skill in the art to use a hydrophobic therapeutic agent, bromfenac, with the elected surfactant. The motivation comes from

the teaching of Chen et al. that a variety of PEG-fatty acid esters have useful surfactant properties. Among the PEG-fatty acid monoesters, esters of lauric acid, oleic acid, and stearic acid are most useful. Hence, a skilled artisan would have reasonable expectation of successfully producing a composition with the most useful surfactant properties.

With respect to claim 19, the transitional phrase “consisting essentially of” limits the scope of a claim to the specified materials or steps “and those that do not materially affect the basic and novel characteristic(s)” of the claimed invention. In re Herz, 537 F.2d 549, 551-52, 190 USPQ 461, 463 (CCPA 1976). “A consisting essentially of' claim occupies a middle ground between closed claims that are written in a consisting of' format and fully open claims that are drafted in a comprising' format.” PPG Industries v. Guardian Industries, 156 F.3d 1351, 1354, 48 USPQ2d 1351, 1353-54 (Fed. Cir. 1998). See also Atlas Powder v. E.I. duPont de Nemours & Co., 750 F.2d 1569, 224 USPQ 409 (Fed. Cir. 1984); In re Janakirama-Rao, 317 F.2d 951, 137 USPQ 893 (CCPA 1963); Water Technologies Corp. vs. Calco, Ltd., 850 F.2d 660, 7 USPQ2d 1097 (Fed. Cir. 1988). For art purposes, “the consisting essentially of” language in the claim is treated as “comprising” language and it is an applicant's burden to establish that a step practiced in a prior art method is excluded from his claims by consisting essentially of' language.” (See MPEP 2111.03)

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim 7 is rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 5, and 47-48 of copending Application No. 11755662 in view of Chen et al. (US 6383471), as applied to claims 1, 4-5, 8, 10-12, 19-20, 22, and 27 above and further in view of Fukahori et al. (JP 402083323A). Although the conflicting claims are not identical, they are not patentably distinct from each other because the copending application is drawn to a method of treating pain and/or inflammation associated with an ocular disease, injury or disorder comprising administering to a patient, in need of such treatment, a stabilized aqueous liquid solution comprising 2-amino-3-(4-bromobenzoyl) phenylacetic acid or a pharmaceutically acceptable salt thereof or a hydrate thereof at a concentration ranging from 0.05% to 0.1% administered once or twice a day, or at a concentration ranging from 0.12% to 0.24% administered once a day, and an alkyl aryl polyether alcohol type polymer whereas the claims herein are drawn to an aqueous liquid preparation comprising 2-amino-3-(4- bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof, and an alkyl aryl polyether alcohol type polymer or a polyethylene glycol fatty acid ester.

Copending Application No. 11755662 and Chen et al. (US 6383471) are discussed above.

Copending Application No. 11755662 and Chen et al. (US 6383471) fail to teach the amount of the polyethylene glycol as claimed.

Fukahori et al. teaches a stable aqueous solution of riboflavin containing non-ionic surfactants preferably polyoxyethylene hardened castor oil or polyethylene glycol monostearate in an amount of 0.01 to 5.0 wt %/vol%.

In the absence of showing the criticality, the determination of optimal or workable concentration of the polyethylene glycol monostearate by routine experimentation is obvious absent showing of criticality of the claimed concentration. One having ordinary skill in the art would have been motivated to do this to obtain the **desired stability and solubilizing** properties of the composition. Hence, a skilled artisan would have had reasonable expectation of successfully producing a composition with the polyethylene glycol monostearate in the claimed range.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 9-10, 13, 21, and 23-25 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 5, and 47-48 of copending Application No. 11755662 in view of Chen et al. (US 6383471), as applied to claims 1, 4-5, 8, 10-12, 19-20, 22, and 27 above and further in view of Gamache et al. (WO 01/15677) and Yakuji Nippo Ltd., ("New Drugs in Japan: 2001", 2001 Edition, Published by May 11, 2001, p.27-29 - IDS). Although the conflicting claims are not identical, they are not patentably distinct from each other because the copending application is drawn to a method of treating pain and/or inflammation associated with an ocular disease, injury or disorder comprising administering to a patient, in need of such treatment, a stabilized aqueous liquid solution comprising 2-amino-3-(4-

bromobenzoyl) phenylacetic acid or a pharmaceutically acceptable salt thereof or a hydrate thereof at a concentration ranging from 0.05% to 0.1% administered once or twice a day, or at a concentration ranging from 0.12% to 0.24% administered once a day, and an alkyl aryl polyether alcohol type polymer whereas the claims herein are drawn to an aqueous liquid preparation comprising 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof, and an alkyl aryl polyether alcohol type polymer or a polyethylene glycol fatty acid ester.

Copending Application No. 11755662 and Chen et al. (US 6383471) are discussed above.

Copending Application No. 11755662 and Chen et al. (US 6383471) fail to teach the specified preservative and stabilizer; and sodium salts and hydrates thereof; or an eye drop.

Gamache et al. teaches anti-inflammatory agents include bromfenac and Moxifloxacin, viscosity building agents include, for example, polyvinyl alcohol, polyvinyl pyrrolidone, methyl cellulose, hydroxypropyl methylcellulose, hydroxyethyl cellulose, carboxymethyl cellulose, hydroxypropyl cellulose or other agents known to those skilled in the art. An appropriate buffer system (e. g., sodium phosphate, sodium acetate or sodium borate) may be added to prevent pH drift under storage conditions. Exemplified is an otic/nasal suspension: lngredient 1B/1 D agonist 0.1-1.0% w/v, Moxifloxacin 0.3% w/v, Benzalkonium Chloride 0.01% w/v, Edetate Disodium, USP 0.01% w/v, Sodium

Chloride, USP 0.3% w/v, Sodium Sulfate, USP 1.2% w/v, Tyloxapol, USP 0.05% w/v, Hydroxyethylcellulose 0.25% w/v, Sulfuric Acid and/or Sodium Hydroxide, NF q. s., and purified water q. s. to 100%.

Yakuji Nippo Ltd. teaches an aqueous ophthalmic solution comprising bromfenac sodium hydrate boric acid, sodium sulfite, disodium edetate, polyvinylpyrroldione, benzalkonium sodium hydrate.

It would have been obvious to one of ordinary skill in the art at the time of the invention to use the specific preservative Benzalkonium Chloride and stabilizer - sodium sulfite. The motivation comes from the teaching of Gamache et al. that the preservatives inclusive of Benzalkonium Chloride prevent microbial contamination during use and the stabilizer prevent pH drift under storage conditions and further by Yakuji Nippo Ltd. that an ophthalmic solution of bromfenac sodium hydrate comprises boric acid, sodium sulfite, disodium edetate, polyvinylpyrroldione, benzalkonium sodium hydrate. Hence, a skilled artisan would have had reasonable expectation of successfully producing a composition with similar efficacy and results.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim 14 is rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 5, and 47-48 of copending Application No. 11755662 in view of Chen et al. (US 6383471), as applied to claims 1, 4-5, 8, 10-12, 19-20, 22, and 27 above and further in view of Sawa (5942508). Although the conflicting claims are not identical, they are not patentably distinct from each other

because the copending application is drawn to a method of treating pain and/or inflammation associated with an ocular disease, injury or disorder comprising administering to a patient, in need of such treatment, a stabilized aqueous liquid solution comprising 2-amino-3-(4-bromobenzoyl) phenylacetic acid or a pharmaceutically acceptable salt thereof or a hydrate thereof at a concentration ranging from 0.05% to 0.1% administered once or twice a day, or at a concentration ranging from 0.12% to 0.24% administered once a day, and an alkyl aryl polyether alcohol type polymer whereas the claims herein are drawn to an aqueous liquid preparation comprising 2-amino-3-(4- bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof, and an alkyl aryl polyether alcohol type polymer or a polyethylene glycol fatty acid ester.

Copending Application No. 11755662 and Chen et al. (US 6383471) are discussed above.

Copending Application No. 11755662 and Chen et al. (US 6383471) fails to a nose drop.

Sawa teaches an aqueous solution comprising a pyridonecarboxylic acid selected from the group consisting of lomefloxacin, norfloxacin, enoxacin, ofloxacin, ciprofloxacin, tosufloxacin, fleroxacin, cinoxacin, levofloxacin and sparfloxacin or a pharmacologically acceptable salt thereof in a concentration of 0.2-5.0 (w/v)%, and an arylcarboxylic acid selected from the group consisting of pranoprofen, ibuprofen, bromfenac, 2-naphthoic acid, 2-naphthylacetic acid and 2-naphthoxyacetic acid or a

pharmacologically acceptable salt thereof in a proportion of 0.001-50 parts by weight per part by weight of the pyridonecarboxylic acid (see claim 2). The reference further teaches examples of the solubilizer include non-ionic surfactants such as polyoxyethylenesorbitane monoolate, polyoxyethyleneoxystearic acid triglyceride, polyethylene glycol, polyoxyethylene hydrogenated castor oil and the like, (col 8 lines 66-67 and col 9 lines 1-3). The aqueous solution of the present invention is used as an eye drop, nasal drop or ear drop. When it is used as an eye drop, its pH is generally adjusted to about 3.5-8.5, preferably about 6-8, when it is used as a nasal drop, its pH is generally adjusted to about 3.5-8.5, preferably about 6-8, (See claims 3-5). Examples of the antiseptic include quaternary ammonium salts such as benzalkonium chloride. Examples of the thickener include polyvinylpyrrolidone, Examples of the chelating agent include sodium edetate, pH adjusting agents include sodium hydroxide, the reference teaches boric acid.

It would have been obvious to one of ordinary skill in the art to use the formulation as a nasal drop. The motivation comes from the teaching of Sawa that an aqueous solution comprising bromfenac is used as an eye drop, nasal drop or ear drop. When it is used as an eye drop, its pH is generally adjusted to about 3.5-8.5, preferably about 6-8, when it is used as a nasal drop, its pH is generally adjusted to about 3.5-8.5, preferably about 6-8. Hence, a skilled artisan would have reasonable expectation of successfully producing a composition with similar efficacy and results.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim 16 is rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 5, and 47-48 of copending Application No. 11755662 in view of Chen et al. (US 6383471) and Fukahori et al. (JP 402083323A), as applied to claims 1, 4-5, 7-8, 10-12, 19-20, 22, and 27 above and further in view of Aikawa et al. (JP 2002308764 A). Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims are drawn to an aqueous solution preparation according to claim 1, wherein the concentration of the aminoglycoside antibiotic or its pharmacologically acceptable salt in the aqueous solution preparation is within a range from a minimum of 0.01 w/v % to a maximum of 35.0 w/v %, and the concentration of the bromfenac or its pharmacologically acceptable salt in the aqueous solution preparation is within a range from a minimum of 0.01 w/v % to a maximum of 0.5 w/v %; further comprising at least one compound selected from the group consisting of a nonionic water-soluble polymer and a nonionic surfactant whereas the claims herein are drawn to an aqueous liquid preparation comprising 2-amino-3-(4- bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof, and an alkyl aryl polyether alcohol type polymer or a polyethylene glycol fatty acid ester.

U.S. Patent No. 5942508, Chen et al. (US 6383471), and Fukahori et al. (JP 402083323A) are discussed above.

U.S. Patent No. 5942508 and Chen et al. (US 6383471), and Fukahori et al. (JP 402083323A) fail to teach the specified sodium salt or a hydrate.

Aikawa et al. teaches ophthalmic pharmaceutical composition (eye drop) for treating or preventing congestion symptom of a conjunctiva, contains bromfenac sodium hydrate.

It would have been obvious to one of ordinary skill in the art to use the sodium salt and hydrate of bromfenac. The motivation comes from the teaching of Aikawa et al. that an aqueous solution (eye drop) comprising bromfenac sodium hydrate treats or prevents congestion symptom of a conjunctiva. Hence, a skilled artisan would have reasonable expectation of successfully producing a composition with similar efficacy and results.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

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 Monday through Friday from 8:30 a.m. to 5:00 p.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).

/Layla Soroush/

Examiner, Art Unit 1627

Notice of References Cited	Application/Control No. 13/353,653	Applicant(s)/Patent Under Reexamination SAWA ET AL.	
	Examiner LAYLA SOROUSH	Art Unit 1627	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
*	A	US-6,383,471	05-2002	Chen et al.	424/45
*	B	US-5,942,508	08-1999	Sawa, Shirou	514/235.8
*	C	US-6,274,592	08-2001	Sawa, Shirou	514/291
*	D	US-2001/0056098	12-2001	Sawa, Shirou	514/258
	E	US-			
	F	US-			
	G	US-			
	H	US-			
	I	US-			
	J	US-			
	K	US-			
	L	US-			
	M	US-			

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	Classification
	N	JP 02083323 A	03-1990	Japan	FUKAHORI et al.	
	O	JP 2002308764 A	10-2002	Japan	OKUDAIRA et al.	
	P	WO 0115677 A2	03-2001	World Intellect	GAMACHE D A et al.	
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	
	V	
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	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
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(54) Title: USE OF 5-$HT_{1B/1D}$ AGONISTS TO TREAT OTIC PAIN

(57) Abstract: Compositions and methods for treating otic pain are disclosed. In particular, the invention discloses compositions and methods of using 5-$HT_{1B/1D}$ agonists for the prevention or alleviation of otic pain.

Use of 5-$HT_{1B/1D}$ Agonists to Treat Otic Pain

The present invention relates to the pharmaceutical treatment of otic pain. In particular, the present invention relates to the topical use of 5-$HT_{1B/1D}$ receptor agonists and partial agonists for the prevention or alleviation of pain in the ear.

Background of the Invention

Pain is a perceived nociceptive response to local stimuli in the body. The perception of pain at the level of the central nervous system requires the transmission of painful stimuli by peripheral sensory nerve fibers. Upon stimulation of tissue (i.e., thermal, mechanical or chemical), electro-chemical signals are transmitted from the sensory nerve endings to the spinal column, and hence to the brain where pain is perceived.

The ear is highly innervated with sensory afferents capable of transmitting various painful stimuli to the central nervous system. The ear is comprised of outer, middle and inner ear portions and otic pain may arise in any of these portions of the ear. Pain conditions involving the ear, therefore, can arise in numerous instances, such as: foreign body stimulus, inflammation, edema, otic congestion, otic pressure, infection, accidental trauma, surgical procedures and post-surgical recovery.

The outer or "external" ear is comprised of the pinna and external ear canal ("EAC"). The EAC is a tubular, slightly curved structure extending from the pinna to the tympanic membrane or "ear drum." Sound travels through the EAC and causes the tympanic membrane to vibrate. Various disorders can arise in the outer ear eliciting pain to the host. For example, otitis externa is an acute, painful inflammatory condition of the EAC that

affects all age groups of humans and accounts for roughly half of the ear pain pathologies known to exist. During the summer months, cases of otitis externa tend to increase due to what is known as "swimmer's ear." Swimmer's ear generally arises from the seepage of water into the EAC during swimming and the onset of infection and pain. Other outer ear disorders causing pain to the host include insertion of foreign objects in the ear, cerumen impaction, long-term use of hearing aids, and dermatological disorders, including psoriasis, eczema and seborrhea.

The middle ear is an air-filled cavity between the outer and inner ears. The middle ear is separated from the outer ear by the tympanic membrane and abuts the inner ear. It has a volume of about two milliliters and is connected to the back of the throat via the eustachian tube. The middle ear contains the malleus, icus and stapes, which are tiny bones that translate the movement of the tympanic membrane to the inner ear. Various conditions of the middle ear can cause pain to the host. For example, otitis media, which can be acute ("AOM") or associated with effusion ("OME"), is an inflammatory condition of the middle ear which generally affects children more often than adults (Karver, *Otitis Media*, Primary Care, Volume 25, No. 3, pages 619-632 (1998). The etiology of otitis media is fairly broad and can be caused by various inflammatory events including infection and allergy. Effusion, which can be sterile or contain infectious material, may also result from otitis media. The fluid consists of various inflammatory cells (white blood cells), mediators of allergy and inflammation and cellular debris.

The inner ear comprises the sensory organs of the auditory and vestibular systems. It consists of two major compartments, known as the bony and membranous labyrinths. These chambers are highly organized and sensitive tissues and provide both auditory perception and

balance to the animal. Various pathologies may arise in the inner ear, creating distortion of hearing, loss of balance and pain.

Since otic pain is often associated with infection and resultant congestion and pressure, the primary therapeutic approach to treating otic pain is the administration of antiobiotics, both systemically and topically.

Various other therapies have been attempted for the alleviation of otic pain. Topical steroids (e.g., hydrocortisone) and systemic non-steroidal anti-inflammatory drugs (NSAIDs), such as aspirin and ibuprofen, have been used typically in conjunction with anti-infectives to treat otic pain.

Local anesthetics are another class of compounds which relieve pain by directly inhibiting nerve cellular function. A drawback of local anesthetic therapy is the short duration of action of such drugs. Another problem with the use of local anesthetics is that their mechanism of action, non-specific membrane stabilization, can have the undesired coincident effect of also inhibiting biological functions of cells, such as fibroblasts and surrounding neural cells. Therefore, even though pain sensation can be abated with local anesthetic treatment, healing and normal function of the tissue may be significantly compromised. There is a need, therefore, to discover agents which potently and specifically inhibit the transmission of painful stimuli by sensory afferents, following local otic application.

Opiates are a class of compounds with well documented clinical analgesic efficacy. Opiates can be administered in a number of ways. For example, opiates can be administered systematically, by intravenous injection or oral dosage, or locally, by subcutaneous, intramuscular or topical application. Systemic administration of opiates, however, has been

associated with several problems including dose escalation (tolerance), addiction, respiratory depression and constipation.

Other agents have also been suggested for use in treating pain. Such agents include tricyclic antidepressants such as imipramine and desipramine, alpha-2 adrenergic agonists, serotonin uptake blockers, such as prozac, and other analgesics such as paracetamol, as described in United States Patent No. 5,270,050 (Coquelet et al.). Some of these therapies, however, have been associated with side-effects such as dryness of mouth, drowsiness, constipation, and low potencies and efficacies.

A class of agents which potently and specifically inhibit the transmission of painful stimuli by sensory afferents without local anesthetic activity following local otic application has yet to be described.

Serotonin, or 5-hydroxytryptamine ("5-HT"), is an endogenous peripheral and central neurotransmitter. Activation of serotonin receptors elicits the transduction of specific intracellular signals which lead to various physiological responses, depending on the receptor sub-type activated and the tissue stimulated. Certain classes of molecules have been discovered which bind to 5-HT receptors and either elicit 5-HT agonist or antagonist responses. Researchers have pursued the use of various 5-HT receptor agonists and antagonists in an effort to modulate cellular activity, and hence, effect various therapies to the afflicted tissues.

A number of different sub-types of 5-HT receptors have been discovered, based on differential agonist/antagonist sensitivities, second messenger coupling and protein structures. Such sub-types include, for example, 5-HT_{1B}, 5-HT_{1D}, 5-HT_{1A} and 5-HT_{2A} (Hoyer et al., *VII. International Union of Pharmacology Classification of Receptors for 5-Hydroxytryptamine (Serotonin)*, Pharmacological Reviews, volume 46, No. 2, Pages 157-170 (1994)). While all

serotonin receptors bind serotonin, different sub-types of serotonin receptors, which demonstrate a selective sensitivity to different agonists and antagonists, exist in various tissues and species. As noted by Hoyer et al. (1994), there are significant differences in the types of serotonin receptors evident among various species. For example, the 5-HT_{1B} receptor exists in rodents, while the homolog of this receptor, the pharmacologically defined 5-HT_{1D} receptor, exists in canine, pig and human species (Adham et al., *The Rat 5-Hydroxytryptamine1B Receptor Is the Species Homologue of the Human 5-Hydroxytryptamine1Dß Receptor*, Molecular Pharmacology, volume 41, pages 1-7 (1992) and Hoyer et al., *VII. International Union of Pharmacology Classification of Receptors for 5-Hydroxytryptamine (Serotonin)*, Pharmacological Reviews, volume 46, no. 2, pages 157-170 (1994)).

Numerous therapeutic approaches involving the manipulation of various serotonin receptors have been attempted. For example, the use of 5-HT_3 antagonists to treat emesis in cancer chemotherapy patients is disclosed in U.S. Patent No. 5,446,050 (Rosen); the use of certain 5-HT_1 agonists to treat a myriad of ailments is disclosed in U.S. Patent No. 5,409,941 (Nowakowski); and the use of 5-HT_2 antagonists to treat CNS disorders such as anxiety have been disclosed in U.S. Patent No. 5,393,761 (Perregaard et al.). However, nowhere in these publications has it been disclosed to use 5-HT_{1B} or 5-HT_{1D} agonists for the treatment of otic pain.

Summary of the Invention

The present invention is directed to compositions and methods of treating otic pain. More specifically, the present invention provides compositions containing 5-HT_{1D} and/or 5-

HT_{1B} agonists for the treatment of otic pain. The present invention is also directed to compositions comprising combinations of 5-HT_{1D} and/or HT_{1B} agonists and other pharmaceutical agents (i.e., anti-microbial agents, anti-inflammatory agents or anti-allergy agents) and methods of use.

The methods of the present invention involve the topical otic or intranasal application of the compositions of the present invention. One advantage of this therapy is that the inhibition of pain is receptor-specific, as contrasted with non-specific therapy, such as local anesthetic treatment. This specific activity may reduce greatly the number of dosings per day, and also reduce the drawbacks of short duration of action and inhibition of wound healing which are associated with local anesthetics. Additionally, serotonin receptor binding agents acting locally within otic tissue avoid the problems of tolerance, addiction and constipation associated with the chronic, systemic administration of opiates.

Detailed Description of the Invention

The present invention is directed to the use of 5-HT_{1D} and/or 5-HT_{1B} receptor agonists for the prevention or alleviation of otic pain. The 5-HT_{1D} ("1D") receptor is found in human tissue such as cerebral arteries and parts of the brain, such as the basal ganglia, raphe and the cerebral cortex (Hoyer et al., (1994)). The 5-HT_{1B} ("1B") receptor, thus far, has been found in the CNS and peripheral nerves of other species such as rat, mouse and hamster. However, the 1B receptor has been shown to possess similar homology, and thus similar sensitivity, as the 1D receptor (Hoyer et al., (1994)). It has now been found that 1B receptor agonists will activate 1D receptors. It is believed that the 5-HT_{1B} and/or 5-HT_{1D} receptors are present in otic tissue.

The compounds of the present invention are 1D agonists, 1B agonists or 1B/1D agonists. As used herein, a "1B agonist" refers to a compound which activates a 1B receptor, a "1D agonist" refers to a compound which activates a 1D receptor, and a "1B/1D agonist" refers to a compound which activates either a 1B or a 1D receptor.

Preferred 1B/1D agonists of the present invention are: 7-trifluoromethyl-4(4-methyl-1-piperazinyl)-pyrrolo[1,2-a]quinoxaline maleate (CGS-12066A); Anpirtoline; RU-24969; 5-carboxamidotryptamine (5-CT); 5-methoxy-n,n,dimethyl-tryptamine; 1H-Indole-5-methanesulfonamide, 3-[2-(dimethylamino)ethyl]-N-methyl- ,butanedioate (Sumatriptan (GR43175C)); Methanesulfonamide,N-[4-[[5-[3-(2-aminoethyl)-1H-indol-5-yl]-1,2,4-oxadiazol- 3-yl]methyl]phenyl] (L-694247); Metergoline; LY165163 (PAPP); BMS-180048; PNU-142633; 1H-2-Benzopyran-6-carboxamide, 3,4-dihydro-1-[2-[4-(4-methoxyphenyl)-1-piperazinyl]ethyl]-N-methyl-, (S) -, (PNU-109291); 5(R)-(methylamino)-2,4,5,6-tetrahydro-1H-imidazo[4,5,1-ij]-quinolin-2- onemaleate (PNU-95666); N-[4-methoxy-3-(4-methyl-1-piperazinyl)phenyl[-4-(2-phenylethyl)-1-piperazinecarboxaminde (F-14258); F-12640, which is a 4-aryl-1-(tryptamine-5-0-carboxymethyl)-piperazide; ALX-0646; 1H-Carbazole-6-carboxamide, 2,3,4,9-tetrahydro-3-(methylamino)-, (R) (frovatriptan); 1H-Indole, 3-((1-methyl-2-pyrrolidinyl)methyl)-5-(2-(phenylsulfonyl)ethyl)-(R) (eletriptan); Pyrrolidine, 1-(((3-(2-(dimethylamino)ethyl)-1H-indol-5-yl)methyl)sulfonyl) (almotriptan); 1H-Indole-3-ethanamie,N,N-dimethyl-5-(1H-1,2,4-triazol-1-ylmethyl)-,monobenzoate (rizatriptan benzoate); 1H-Indole-5-ethanesulfonamide, N-methyl-3-(1-methyl-4-piperidinyl) (naratriptan); 2-Oxazolidinone, 4-((3-(2-(dimethylamino)ethyl)-1H-indol-5-yl)methyl)-, (S) (zolmitriptan); Glycinamide, N-[[[3-(2-aminoethyl)-1H-indol-5-yl]oxy]acetyl]-L-tyrosyl- (IS-159); 1'-Methyl-5-[2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)-biphenyl-4-ylcarbonyl]-2,3,6,7-tetrahydro-5H-spiro[furo[2,3-f]indole-3,4'-piperidine] (SB-224289); L-782097; 3-[3-

[4-(5,6-Dimethoxypyrimidin-4-yl)piperazin-1-yl]propyl]-N-methyl-1H-indol- 5-ylmethylsulfonamide (VS-395); (R)-N-methyl-[3-(1-methyl-2-pyrrolidinyl)-1H-indol-5-yl]methanesulphonamide (CP-122288); 3-[3-[4-(5-methoxy-4-pyrimidinyl)-1-piperazinyl]-propyl]-N-methyl-1H-indole-5- 5-methanesulfonamide (avitriptan); Piperazine, 1-(2,3-dihydro-1,4-benzodioxin-5-yl) (eltoprazine); N-[3-(2-dimethylamino)ethoxy-4-methoxyphenyl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)-(1,1'-biphenyl)-4-carboxamide (SB-216641); and 3-[4-(3-chlorophenyl) piperazin-1-yl]-1,1-diphenyl-2-propanol) (BRL-15572).

Other classes of 1B/1D agonists have been suggested or are known in the art and may be useful in the present invention. For example, U.S. Patent Nos. 5,504,104 (Glennon) and 5,252,749 (Badorc et al.) disclose tryptamine analogs and thienocyclopentanone oxime ethers, respectively, and WIPO Patent Publication No. WO 95/14004 (Halazy et al.) discloses azylpiperazines, for use as 1B/1D agonists; the foregoing patents and publication are incorporated herein by reference to the extent they disclose 1B, 1D or 1B/1D agonists and methods of preparation or attainment. The 1B/1D agonists of the present invention are available from commercial sources or may be synthesized by methods known to those skilled in the art.

The 1B/1D agonists of the present invention may also be elucidated by employing standard methods known in the art. For example, the 1B/1D compounds may be ascertained by using radioligand binding assays to determine drug affinities at the $5HT_{1B/D}$ receptor such as those described in Hoyer, et al., *Characterization of the $5HT_{1B}$ recognition sites in rat brain: binding studies with (-)-[^{125}I]cyanopindolol*, Eur. J. Pharmacol., volume 118, pages 1-12 (1985). The 1B/1D compounds may also be determined using a number of functional *in vitro* assays. Common assays include methods involving the inhibition of forskolin-induced

adenylyl cyclase activity in (1) cells that naturally express the $5HT_{1B/D}$ receptor (e.g., in Chinese hamster ovary cells as described in Giles, et al., *Characterization of a 5HT1B receptor in CHO cells: functional responses in the absence of radioligand binding*, Br. J. Pharmacol., volume 117, pages 1119-1126 (1996)), and (2) in host cells genetically engineered to express recombinant human or animal $5HT_{1B/D}$ receptors (e.g., Price, et al., *SB-216641 and BRL-15572 compounds to pharmacologically discriminate h5HT$_{1B}$ and h5HT$_{1D}$ receptors*, Naunyn-Schmiedeburg's Arch. Pharmacol., volume 356, pages 312-320 (1997)). In addition, intercellular Ca^{2+}-mobilization assays have also been employed to determine the efficacy of 1B/1D compounds for agonist activity at the $5HT_{1B/D}$ receptor (Dickenson and Hill, *Coupling of an endogenous 5HT1B-like receptor to increases in intracellular calcium through a pertussis toxin-sensitive mechanism in CHO-K1 cells*, Br. J. Pharmacol., volume 116, pages 2889-2896 (1995)). Assays involving the functional activity *in vivo* at the $5HT_{1B/D}$ receptor are also useful for the determination 1B/1D compounds. For example, Matsubara et al. describe a method to elucidate 1B/1D compounds using the electrically-induced neurogenic plasma extravasation from the brain dura matter by stimulation of the trigeminal ganglion (Matsubara, et al., *CP-93,129, a potent and selective 5HT$_{1B}$ receptor agonist blocks neurogenic plasma extravasation within rat but not in guinea pig dura matter*, Br. J. Pharmacol., volume 104, pages 3-4 (1991)).

The 1B/1D agonists of the present invention will be contained in topical or intranasal compositions, in accordance with formulation techniques known to those skilled in the art. The compounds may be included in solutions, suspensions, aerosols and other dosage forms adapted for the particular 1B/1D agonist and dosing regimen.

The 1B/1D compounds will be contained in compositions of the present invention in concentrations effective to prevent or ameliorate otic pain. As used herein, the term

"pharmaceutically effective amount" refers to that amount of one or more 1B/1D agonists which prevents or alleviates otic pain. Generally, the dosage of 1B/1D agonists utilized for any of the uses described herein will be from about one to two drops of a 0.01 to 3% weight/volume ("% w/v") composition, or corresponding amount for aerosol application, administered one to four times per day.

The present invention is particularly directed to the provision of compositions adapted for topical treatment of otic tissues. The compositions may also be adapted for administration intranasally for treatment of otic tissues, such as nasal drops or an aerosol composition. The otic compositions of the present invention will include one or more 1B/1D agonists and a pharmaceutically acceptable vehicle for these agonist(s). Various types of vehicles may be used. The vehicles will generally be aqueous in nature. Aqueous solutions or suspensions are generally preferred, based on ease of formulation, as well as a patient's ability to easily administer such compositions by means of instilling one to two drops of the solutions in the affected ears. However, the compounds of the present invention may also be readily incorporated into other types of compositions, such as aerosols (intranasal or intraotic), suspensions, viscous or semi-viscous gels or other types of solid or semi-solid compositions. Suspensions may be preferred for 1B/1D agonists which are relatively insoluble in water.

As stated above, the compositions of the present invention may also contain additional pharmaceutically active agents or may be dosed concurrently with other pharmaceutical compositions.

In particular, when treating a mammal for the prevention, treatment or amelioration of otic infection, the compositions of the present invention may also contain one or more antibiotic, antiviral and/or antifungal agents (hereinafter collectively referred to as "anti-microbial agents") or may be dosed concurrently or sequentially with anti-microbial agent

containing compositions. Examples of anti-microbial agents include, but are not limited to, chloremphenicol, ofloxacin, norfloxacin, lomefloxacin, ciprofloxacin, natamycin, neomycin, polymyxin B, gentamycin, tobramycin, bacitracin, gramicidin, erythromycin, moxifloxacin, oxazolidinones, trovafloxacin, grepafloxacin, sulfacetamide, tetracycline, sulfisoxazole, diolamine, trifluorothymidine, acyclovir, gancyclovir, vaniomycin or other antibiotic, antiviral and antifungal agents known to those skilled in the art. The 1B/1D agonist/anti-microbial agent combination compositions will contain one or more 1B/1D agonists, as stated above, and one or more anti-microbial agents in an amount effective to prevent, treat or ameliorate otic infection. As used herein, such an amount is referred to as "an effective amount of one or more anti-microbial agents" or "an amount effective to prevent, treat or ameliorate otic infection." In general, however, the 1B/1D agonist/anti-microbial combination compositions of the present invention will typically contain one or more antibiotics in an amount of about 0.05 to 3.0 % w/v.

When treating a mammal for the prevention, treatment or amelioration of otic allergic reactions and responses, the compositions of the present invention may also contain one or more anti-allergy agents, histamine H_1 receptor antagonists or anti-histaminic agents (hereinafter collectively referred to as "anti-allergy agents"), or may be dosed concurrently or sequentially with anti-allergy agent containing compositions. Examples of anti-allergy agents include, but are not limited to, mizolastine, mapinastine, levocabastine, pheniramine, antazoline, ketotifen, azelastine, doxepine analogs, such as those described in U.S. Patent Nos. 4,871,865 (Lever et al.) and 4,923,892 (Lever et al.), cetirizine, loratadine, fenoxifenadine, diphenhydramine, brompheniramine, chlorpheniramine, clemastine, pyrilamine, cromolyn, nedocromil, lodoxamide, or other anti-allergy agents known to those skilled in the art. The 1B/1D agonist/anti-allergy agent combination compositions will contain

one or more 1B/1D agonists, as stated above, and one or more anti-allergy agents in an amount effective to prevent, treat or ameliorate otic allergic reactions and responses. As used herein, such an amount is referred to as "an effective amount of one or more anti-allergy agents" or "an amount effective to prevent, treat or ameliorate otic allergic reactions or responses." In general, however, the 1B/1D agonist/anti-allergy agent combination compositions of the present invention will typically contain one or more anti-allergy agents in an amount of about 0.001 to 1.0 % w/v.

When treating a mammal for the prevention, treatment or amelioration of otic inflammatory reactions and responses, the compositions of the present invention may also contain one or more anti-inflammatory agents or may be dosed concurrently or sequentially with anti-inflammatory agent containing compositions. Examples of anti-inflammatory agents include, but are not limited to, PAF antagonists, such as SR-27417, A-137491, ABT-299, apafant, bepafant, minopafant, E-6123, BN-50727, nupafant and modipafant; PDE IV inhibitors, such as ariflo, torbafylline, rolipram, filaminast, piclamilast, cipamfylline, CG-1088, V-11294A, CT-2820, PD-168787, CP-293121, DWP-205297, CP-220629, SH-636, BAY-19-8004, and roflumilast; cyclooxygenase type I and II inhibitors, such as nepafenac, amfenac, diclofenac, flurbiprofen, indomethacin, naproxen, ketorolac, ibuprofen, bromfenac, ketoprofen, meclofenamate, piroxicam, sulindac, suprofen, mefanamic acid, diflusinal, oxaprozin, tolmetin, fenoprofen, benoxaprofen, nabumetome, etodolac, phenylbutazone, aspirin, oxyphenbutazone, NCX-4016, HCT-1026, NCX-284, NCX-456, tenoxicam and carprofen; cyclooxygenase type II selective inhibitors, such as NS-398, vioxx, celecoxib, P54, etodolac, darbufelone mesylate, L-804600 and S-33516; and inhibitors of cytokine production, such as inhibitors of the NFkB transcription factor; or other anti-inflammatory agents known to those skilled in the art. The 1B/1D agonist/anti-inflammatory agent

combination compositions will contain one or more 1B/1D agonists, as stated above, and one or more anti-inflammatory agents in an amount effective to prevent, treat or ameliorate otic inflammatory reactions and responses. As used herein, such an amount is referred to as "an effective amount of one or more anti-inflammatory agents" or "an amount effective to prevent, treat or ameliorate otic inflammatory reactions or responses." In general, however, the 1B/1D agonist/anti-inflammatory agent combination compositions of the present invention will typically contain one or more anti-inflammatory agents in an amount of about 0.01 to 1.0 % w/v.

The otic compositions of the present invention may also include various other ingredients, such as buffers, preservatives, co-solvents and viscosity building agents.

An appropriate buffer system (e.g., sodium phosphate, sodium acetate or sodium borate) may be added to prevent pH drift under storage conditions.

Otic products are typically packaged in multidose form. Preservatives are thus required in multidose compositions to prevent microbial contamination during use. Suitable preservatives include: benzalkonium chloride, thimerosal, chlorobutanol, methyl paraben, propyl paraben, phenylethyl alcohol, edetate disodium, sorbic acid, polyquaternium-1, or other agents known to those skilled in the art. Such preservatives are typically employed at a level of from 0.001 to 1.0 % w/v.

Some of the compounds of the present invention may have limited solubility in water and therefore may require a surfactant or other appropriate co-solvent in the composition. Such co-solvents include: polyethoxylated castor oils, Polysorbate 20, 60 and 80; Pluronic® F-68, F-84 and P-103 (BASF Corp., Parsippany NJ, USA); cyclodextrin; or other agents known to those skilled in the art. Such co-solvents are typically employed at a level of from 0.01 to 2% w/v.

Viscosity greater than that of simple aqueous solutions may be desirable to increase otic absorption of the active compound, to decrease variability in dispensing the formulations, to decrease physical separation of components of a suspension or emulsion of formulation and/or otherwise to improve the otic formulation. Such viscosity building agents include, for example, polyvinyl alcohol, polyvinyl pyrrolidone, methyl cellulose, hydroxypropyl methylcellulose, hydroxyethyl cellulose, carboxymethyl cellulose, hydroxypropyl cellulose or other agents known to those skilled in the art. Such agents are typically employed at a level of from 0.01 to 2% w/v.

The compositions may also be used for treating irritated tissues following otic surgery. The compositions may be used for acute treatment of temporary conditions, or may be administered chronically. The compositions may also be used prophylactically, especially prior to otic surgery or noninvasive otic procedures, or other types of surgery.

As stated above, the compounds and compositions of the invention will be used to prevent or ameliorate otic pain associated with various stimuli. For example, the 1B/1D agonists and compositions of the present invention may be used in treating pain arising from allergens, inflammation, trauma, congestion, infection, foreign body sensation and surgery, e.g., following cochlear implant surgery. With such treatment, the 1B/1D agonists can be individually dosed, or in combination with other pharmaceutical agents known in the art.

The compositions of the present invention are further illustrated by the following formulation examples 1-4. The ingredient "1B/1D agonist" denotes a compound of the present invention.

Example 1

The following is an example of an otic/nasal solution:

Ingredient	Amount (% w/v)
7-trifluoromethyl-4(4-methyl-1-piperazinyl) -pyrrolo[1,2-a]quinoxaline maleate (CGS-12066A)	0.01-1.0
Phosphate Buffered Saline	1.0
Polysorbate 80	0.5
Purified water	q.s. to 100%

Example 2

The following is an example of an otic/nasal suspension:

Ingredient	Amount (% w/v)
1B/1D agonist	0.01-1.0
Monobasic sodium phosphate	0.05
Dibasic sodium phosphate (anhydrous)	0.15
Sodium chloride	0.75
Disodium EDTA (Edetate disodium)	0.05
Cremophor EL	0.1
Benzalkonium chloride	0.01
HCl and/or NaOH	pH 7.3 - 7.4
Purified water	q.s. to 100%

Example 3

The following is an example of an otic/nasal suspension or solution:

Ingredient	Amount (% w/v)
1B/1D agonist	0.01-1.0
Phosphate Buffered Saline	1.0
Hydroxypropyl-β-cyclodextrin	4.0
Purified water	q.s. to 100%

Example 4

The following is an example of an otic/nasal suspension:

Ingredient	Amount (% w/v)
1B/1D agonist	0.1-1.0
Moxifloxacin	0.3
Benzalkonium Chloride	0.01
Edetate Disodium, USP	0.01
Sodium Chloride, USP	0.3
Sodium Sulfate, USP	1.2
Tyloxapol, USP	0.05
Hydroxyethylcellulose	0.25
Sulfuric Acid and/or	
Sodium Hydroxide, NF	q.s.
Purified Water, USP	q.s. to 100%

What is claimed is:

1. A topical otic or intranasal composition for treating otic pain comprising a pharmaceutically effective amount of one or more 1B/1D agonist(s) in a pharmaceutically acceptable vehicle.

2. A composition according to Claim 1, wherein the 1B/1D agonist is selected from the group consisting of: CGS-12066A; Anpirtoline; RU-24969; 5-carboxamidotryptamine; 5-methoxy-n,n,dimethyl-tryptamine; Sumatriptan; L-694247; Metergoline; LY165163; BMS-180048; PNU-142633; PNU-109291; PNU-95666; F-14258; F-12640; ALX-0646; frovatriptan; eletriptan; almotriptan; rizatriptan benzoate; naratriptan; zolmitriptan; IS-159; SB-224289; L-782097; VS-395; CP-122288; avitriptan; eltoprazine; BRL-15572; and SB-216641.

3. A composition according to Claim 2, wherein the 1B/1D agonist is 7-trifluoromethyl-4(4-methyl-1-piperazinyl)-pyrrolo[1,2-a]quinoxaline maleate.

4. A composition according to Claim 2, wherein the 1B/1D agonist is Anpirtoline.

5. A composition according to Claim 1, wherein the composition also comprises one or more an anti-microbial agents in an amount effective to prevent, treat or ameliorate otic infections.

6. A composition according to Claim 1, wherein the composition also comprises one or more an anti-allergy agents in an amount effective to prevent, treat or ameliorate otic allergy reactions or responses.

7. A composition according to Claim 1, wherein the composition also comprises one or more an anti-inflammatory agents in an amount effective to prevent, treat or ameliorate otic inflammatory reactions or responses.

8. A composition according to Claim 5, wherein the anti-microbial agent(s) is/are selected from the group consisting of: chloremphenicol, ofloxacin, norfloxacin, lomefloxacin, ciprofloxacin, natamycin, neomycin, polymyxin B, gentamycin, tobramycin, bacitracin, gramicidin, erythromycin, moxifloxacin, oxazolidinones, trovafloxacin, grepafloxacin, sulfacetamide, tetracycline, sulfisoxazole, diolamine, trifluorothymidine, acyclovir, gancyclovir and vaniomycin.

9. A composition according to Claim 6, wherein the anti-allergy agent(s) is/are selected from the group consisting of: mizolastine, mapinastine, levocabastine, pheniramine, antazoline, ketotifen, azelastine, doxepine analogs, cetirizine, loratadine, fenoxifenadine, diphenhydramine, brompheniramine, chlorpheniramine, clemastine, pyrilamine, cromolyn, nedocromil and lodoxamide.

10. A composition according to Claim 7, wherein the anti-inflammatory agent(s) is/are selected from the group consisting of: PAF antagonists; PDE IV inhibitors; cyclooxygenase type I and II inhibitors; cyclooxygenase type II selective inhibitors; and inhibitors of cytokine production.

11. A composition according to Claim 10, wherein the PAF antagonists are selected from the group consisting of SR-27417, A-137491, ABT-299, apafant, bepafant, minopafant, E-6123, BN-50727, nupafant and modipafant; the PDE IV inhibitors are selected from the group consisting of ariflo, torbafylline, rolipram, filaminast, piclamilast, cipamfylline, CG-1088, V-11294A, CT-2820, PD-168787, CP-293121, DWP-205297, CP-220629, SH-636, BAY-19-8004 and roflumilast; the cyclooxygenase type I and II inhibitors are selected from the group consisting of nepafenac, amfenac, diclofenac, flurbiprofen, indomethacin, naproxen, ketorolac, ibuprofen, bromfenac, ketoprofen, meclofenamate, piroxicam, sulindac, suprofen, mefanamic acid, diflusinal, oxaprozin, tolmetin, fenoprofen, benoxaprofen, nabumetome, etodolac, phenylbutazone, aspirin, oxyphenbutazone, NCX-4016, HCT-1026, NCX-284, NCX-456, tenoxicam and carprofen; the cyclooxygenase type II selective inhibitors are selected from the group consisting of NS-398, vioxx, celecoxib, P54, etodolac, darbufelone mesylate, L-804600 and S-33516; and the inhibitors of cytokine

production are selected from the group consisting of inhibitors of the NFkB transcription factor.

12. A method for treating otic pain which comprises administering to a mammal a topical or intranasal composition comprising a pharmaceutically effective amount of one or more 1B/1D agonists in a pharmaceutically acceptable vehicle.

13. A method according to Claim 12, wherein the 1B/1D agonist is selected from the group consisting of: CGS-12066A; Anpirtoline; RU-24969; 5-carboxamidotryptamine; 5-methoxy-n,n,dimethyl-tryptamine; Sumatriptan; L-694247; Metergoline; LY165163; BMS-180048; PNU-142633; PNU-109291; PNU-95666; F-14258; F-12640; ALX-0646; frovatriptan; eletriptan; almotriptan; rizatriptan benzoate; naratriptan; zolmitriptan; IS-159; SB-224289; L-782097; VS-395; CP-122288; avitriptan; eltoprazine; BRL-15572; and SB-216641.

14. A method according to Claim 13, wherein the 1B/1D agonist is 7-trifluoromethyl-4(4-methyl-1-piperazinyl)-pyrrolo[1,2-a]quinoxaline maleate.

15. A method according to Claim 14, wherein the 1B/1D agonist is Anpirtoline.

16. A method according to Claim 12, further comprising administering the composition topically to the ear or intranasally.

17. A method according to Claim 13, further comprising administering the composition topically to the ear or intranasally.

18. A method according to Claim 12, wherein the otic pain is caused by otitis media, otitis externa, otic surgery or swimmer's ear.

19. A method according to Claim 12, wherein the composition further comprises one or more anti-microbial agents in an amount effective to prevent, treat or ameliorate otic infections.

20. A method according to Claim 12, wherein the composition further comprises one or more anti-allergy agents in an amount effective to prevent, treat or ameliorate otic allergic reactions or responses.

21. A method according to Claim 12, wherein the composition further comprises one or more anti-inflammatory agents in an amount effective to prevent, treat or ameliorate otic inflammatory reactions or responses.

22. A method according to Claim 19, wherein the anti-microbial agent(s) is/are selected from the group consisting of: chloremphenicol, ofloxacin, norfloxacin, lomefloxacin, ciprofloxacin, natamycin, neomycin, polymyxin B, gentamycin, tobramycin, bacitracin, gramicidin, erythromycin, moxifloxacin, oxazolidinones, trovafloxacin, grepafloxacin, sulfacetamide, tetracycline, sulfisoxazole, diolamine, trifluorothymidine, acyclovir, gancyclovir and vaniomycin.

23. A method according to Claim 20, wherein the anti-allergy agent(s) is/are selected from the group consisting of: mizolastine, mapinastine, levocabastine, pheniramine, antazoline, ketotifen, azelastine, doxepine analogs, cetirizine, loratadine, fenoxifenadine, diphenhydramine, brompheniramine, chlorpheniramine, clemastine, pyrilamine, cromolyn, nedocromil and lodoxamide.

24. A method according to Claim 21, wherein the anti-inflammatory agent(s) is/are selected from the group consisting of: PAF antagonists; PDE IV inhibitors; cyclooxygenase type I and I inhibitors; cyclooxygenase type II selective inhibitors; and inhibitors of cytokine production.

25. A method according to Claim 24, wherein the PAF antagonists are selected from the group consisting of SR-27417, A-137491, ABT-299, apafant, bepafant, minopafant,

E-6123, BN-50727, nupafant and modipafant; the PDE IV inhibitors are selected from the group consisting of ariflo, torbafylline, rolipram, filaminast, piclamilast, cipamfylline, CG-1088, V-11294A, CT-2820, PD-168787, CP-293121, DWP-205297, CP-220629, SH-636, BAY-19-8004 and roflumilast; the cyclooxygenase type I and I inhibitors are selected from the group consisting of nepafenac, amfenac, diclofenac, flurbiprofen, indomethacin, naproxen, ketorolac, ibuprofen, bromfenac, ketoprofen, meclofenamate, piroxicam, sulindac, suprofen, mefanamic acid, diflusinal, oxaprozin, tolmetin, fenoprofen, benoxaprofen, nabumetome, etodolac, phenylbutazone, aspirin, oxyphenbutazone, NCX-4016, HCT-1026, NCX-284, NCX-456, tenoxicam and carprofen; the cyclooxygenase type II selective inhibitors are selected from the group consisting of NS-398, vioxx, celecoxib, P54, etodolac, darbufelone mesylate, L-804600 and S-33516; and the inhibitors of cytokine production are selected from the group consisting of inhibitors of the NFkB transcription factor.

26. A method according to Claim 19, wherein the otic pain is caused by otitis media, otitis externa, otic surgery or swimmer's ear.

27. A method according to Claim 22, wherein the otic pain is caused by otitis media, otitis externa, otic surgery or swimmer's ear.

PAT-NO: JP402083323A
DOCUMENT-IDENTIFIER: JP 02083323 A

TITLE: STABLE AQUEOUS SOLUTION OF RIBOFLAVIN BUTYRATE

PUBN-DATE: March 23, 1990

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APPL-NO: JP63233563
APPL-DATE: September 20, 1988

INT-CL (IPC): A61K031/525 , A61K009/08 , A61K047/32

ABSTRACT:

PURPOSE: To obtain an aqueous solution of riboflavin butyrate, containing the riboflavin butyrate and a nonionic surfactant with a high solubility and improved in stability to heat and light.

CONSTITUTION: An aqueous solution containing riboflavin butyrate and a nonionic surfactant. Polyoxyethylene hardened castor oil is preferred as the nonionic surfactant or polyethylene glycol monostearate, etc., and blended in an amount of 0.01-5.0wt.%/vol.%. Vitamin Es or vegetable oils (e.g., safflower or soybean oil) or both are preferably blended. The amount of the vitamin Es blended is preferably 0.001-0.5wt./vol.%.

Search Notes	Application/Control No.	Applicant(s)/Patent under Reexamination	
	13/353,653	SAWA ET AL.	
	Examiner	Art Unit	
	LAYLA SOROUSH	1627	

SEARCHED			
Class	Subclass	Date	Examiner

INTERFERENCE SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES (INCLUDING SEARCH STRATEGY)		
	DATE	EXMR
STIC : Npl and pat see search his	8/23/2012	LS
odp	8/23/2012	LS

* NOTICES *

DETAILED DESCRIPTION

[Detailed Description of the Invention]
[0001]
[Field of the Invention]The present invention relates to a drug-used-in-ophthalmology constituent. It is related with a drug-used-in-ophthalmology constituent effective in mitigation and removal of the congestion condition of eye membrane in more detail.
[0002]
[Description of the Prior Art]The disease which shows the congestion condition of eye membrane, for example, the conjunctivitis, is an inflammatory disease of eye membrane. Although the causes of the conjunctivitis were various and it was conventionally considered mainly as the condition based on bacterial infection, allergy attracts attention as one of the causes of a disease in recent years. Although there are various causative agents (allergen) of allergy, it is supposed that the fine particles in pollen, house dust, and exhaust gas, a food component, etc. will become allergen.
[0003]Generally, although allergy is considered that a causal therapy is made by removing allergen and the desensitization therapy is also performed, a treatment period becomes long and it has the fault that going-to-hospital-regularly frequency increases. Therefore, the actual condition is that it is difficult for a patient's burden to continue a therapy in everyday life comparatively largely, and it is not easily established as a causal therapy. Therefore, symptomatic therapy cannot but take the lead naturally.
[0004]As symptomatic therapy over various eye membrane congestion, Although removal, mitigation, etc. of removal and mitigation of the bloodshot eyes by a vasoconstrictor, the eye-ache by a local anesthetic, eye itching paraesthesia, and eye displeasure are common, otherwise, Inhibition of the allergic reaction represented by the pollinosis by an antihistaminic agent or removal and mitigation of eye itching paraesthesia, the improvement of the microcirculation by vitamins, the improvement of asthenopia, etc. are known.
[0005]Let it be an important remedial element what to do removal and mitigation of various symptoms, such as congestion of eye membrane, early especially in the therapy of the conjunctivitis etc. Especially, it is important that improving at an early stage is called for and it exerts such a curative effect also in the field of an over-the-counter drug also from a viewpoint that congestion condition including the swelling of eye membrane prevents shift to a critical condition beforehand in view of QOL.
[0006]However, curative effect sufficient in the above symptomatic therapy is not acquired, but an operation and the number of times of transient ****** increase inevitably. Therefore, to develop the ophthalmic solutions or ophthalmic ointments which exerts sufficient curative effect which is not in the conventional symptomatic therapy medicine was desired.
[0007]
[Problem to be solved by the invention]The present invention makes it problem to provide a drug-used-in-ophthalmology constituent effective in reducing and removing the congestion condition of

eye membrane.
[0008]
[Means for solving problem]As a result of inquiring intensively that the aforementioned problem should be solved, the inventors find out that the constituent which blended both vasoconstrictors with bromine FENAKU sodium which is 1 type of a non-steroidal anti-inflammatory drug acts to mitigation and removal of the various symptoms by congestion of eye membrane very effectively, and came to complete the present invention.
[0009]That is, the present invention is a drug-used-in-ophthalmology constituent containing bromine FENAKU sodium and a vasoconstrictor.
[0010]Bromine FENAKU sodium in the present invention may be known as a non-steroidal anti-inflammatory drug, and this may be a salt or a hydrate.
[0011]As a vasoconstrictor of the present invention, tetrahydrozoline, naphazoline, phenylephrine, ephedrine, methylephedrine, and epinephrine may be preferable, and these may be salts. A hydrochloride, a nitrate, etc. can be mentioned as a salt. These vasoconstrictors can also be blended not only combining any 1 type but combining 2 type or more.
[0012]The compounding amount of bromine FENAKU sodium in the drug-used-in-ophthalmology constituent of the present invention and a vasoconstrictor is as follows. In bromine FENAKU sodium, it blends so that it may be set to 0.1-0.5 mg per day, and 0.02-0.15 mg per time. It is because the stimulus to eye membrane may be produced when effect sufficient in less than 0.02 mg per time is not acquired but it exceeds 0.15 mg per time. In a vasoconstrictor, it blends so that it may be set to 0.004-4 mg per day, and 0.001-1.5 mg per time. It is because tolerance may be produced and it is not preferable, if congestion removing effect sufficient in less than 0.001 mg per time is not acquired but it exceeds 1.5 mg.
[0013]
[Mode for carrying out the invention]In addition to the above-mentioned component, other components can be suitably blended with the drug-used-in-ophthalmology constituent in the present invention as occasion demands.
[0014]The drug-used-in-ophthalmology constituent of the present invention can be prepared with a conventional method. For example, it can prepare by dissolving bromine FENAKU sodium and a vasoconstrictor in sterile purified water with an additive agent etc. As an additive agent which can be used for preparation of pharmaceutical preparation, preservatives, such as a surfactant, a solubilizing agent, and a buffer, perfume and a cool-ized agent, pigments (menthol, camphor, etc.), an antiseptic, etc. are mentioned.
[0015]The drug-used-in-ophthalmology constituent of the present invention can be prescribed for the patient by dropping optimum dose at an eye as ophthalmic solutions, or applying optimum dose as an ointment.
[0016]
[Working example]Although an working example and the example of an examination are given to below and the present invention is described still in detail, the present invention is not limited to these.
[0017]
(Working example 1)
Bromfenac sodium hydrate 50mg naphazoline hydrochloride Weighed 2 mg of components [each of] of the diphenhydramine hydrochloride 30mg above, it was made to dissolve in purified water, and the whole quantity was set to 100mL. It filled up the container with this 15 mL at a time, and eye drops were **(ed).
[0018]
(Working example 2)
Bromfenac-sodium-hydrate 100mg DL-methylephedrine hydrochloride 75-mg diphenhydramine hydrochloride Weighed 50 mg of components [each of] of the cyanocobalamine 20mg above, it was

made to dissolve in purified water, and the whole quantity was set to 100mL. It filled up the container with this 15 mL at a time, and eye drops were **(ed).
[0019]
(Working example 3)
Bromfenac sodium hydrate 100mg tetracaine hydrochloride 50mg chlorpheniramine maleate Weighed 30 mg of components [each of] of the potassium L-aspartate 1g above, it was made to dissolve in purified water, and the whole quantity was set to 100mL. It filled up the container with this 15 mL at a time, and eye drops were **(ed).
[0020]
(Working example 4)
Bromfenac sodium hydrate 100mg epinephrine hydrochloride 3mg chlorpheniramine maleate 300mg sodium chondroitin sulfate Weighed 500 mg of components [each of] of the pyridoxine hydrochloride 50mg above, it was made to dissolve in purified water, and the whole quantity was set to 100mL. It filled up the container with this 15 mL at a time, and eye drops were **(ed).
[0021]
(Working example 5)
Sulfamethoxazole 3g bromfenac sodium hydrate 100mg phenylephrine hydrochloride 100mg ketotifen fumarate 25 mg Flavin adenine dinucleotide sodium 50 mg of components [each of] of the aminoethylsulfonic acid 1g above are weighed, It was made to dissolve in purified water and the whole quantity was set to 100mL. It filled up the container with this 15 mL at a time, and eye drops were **(ed).
[0022]
(Working example 6)
Bromfenac sodium hydrate 100 mg. Naphazoline hydrochloride 3 mg Neostigmine methylsulfate . 3mg diphenhydramine hydrochloride 50mg sodium chondroitin sulfate 300mg tocopherol acetate 50mg L-menthol each of components of the methyl parahydroxybenzoate 30mg above 500 mg of propylene glycol 10 mg. After weighing and mixing uniformly, the ointment base (PURASUBECHI base) was made to distribute and suspend, and the whole quantity was 100 g at it. The container was filled up with this and the ophthalmic ointment was **(ed).
[0023](Example of an examination) [A remission operation on the rabbit eye membrane congestion reaction of combination pharmaceutical preparation]
Two drops applied eyewash in capsaicin liquid 3.0% previously, and the congestion condition of eye membrane was made to cause each three groups using a 12-week old Japanese white male rabbit. According to the formula (inside of 100mL) of the Table 1 description, eyewash was applied to this in two drops of drugs, respectively, and the congestion removing effect after after-instillation 1 temporal passage was compared with it. The standard of the following three-stage was made into the index, and evaluation was performed visually. A result is shown in Table 2.
a valuation basis -- + which is congested crimson and of which ++ congestion is done -- ** which is hardly congested [0024]
[Table 1]

単位：質量％

成分 群	A	B	C	D	E	ｺﾝﾄﾛｰﾙ
塩酸ﾅﾌｧｿﾞﾘﾝ	0.003	—	0.003	—	—	—
塩酸ﾌｪﾆﾚﾌﾘﾝ	—	0.1	—	0.1	—	—
ﾌﾞﾛﾑﾌｪﾅｸﾅﾄﾘｳﾑ水和物	0.1	0.1	—	—	0.1	—

[Table 2]

群	A	B	C	D	E	コントロール
充血症状程度評価	±	±	+	++	++	++

[0025]From Table 2, A and B group surpass more remarkably than other control groups a remission operation on an eye membrane congestion reaction.
It turns out that eye drops concerning the present invention play a remarkable operation in mitigation and a removal action of eye membrane congestion condition as compared with a case where bromfenac sodium hydrate and a vasoconstrictor are used alone.

[0026]
[Effect of the Invention]It became possible to provide the ophthalmic solutions consisting of the drug-used-in-ophthalmology constituent effective in mitigation and removal and this constituent of congestion condition of eye membrane, etc. by the present invention.

[Translation done.]

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of	:	
Shirou SAWA et al.	:	
Serial No. NEW	:	
Filed January 19, 2012	:	
AQUEOUS LIQUID PREPARATION CONTAINING 2-AMINO-3-(4-BROMOBENZOYL)PHENYLACETIC ACID **(Rule 1.53(b) Divisional of Serial No. 10/525,006, Filed March 28, 2005)**	:	Attorney Docket No. 2012_0088

INFORMATION DISCLOSURE STATEMENT

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

Sir:

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

It is requested that the Examiner consider all the information of record in the prior parent application(s) (Serial No. 10/525,006), relied on by the present application under 35 U.S.C. § 120. A copy of any listed reference that was previously cited by or submitted to the PTO in the prior parent application(s) is not required or provided herein (see 37 C.F.R. 1.98(d)).

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 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 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.

Respectfully submitted,

Shirou SAWA et al.

/Warren M. Cheek/

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January 19, 2012

Sheet 1 of 2

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: January 19, 2012	**ATTY DOCKET NO.** 2012_0088	**SERIAL NO.** NEW
	APPLICANT Shirou SAWA et al.	
	FILING DATE January 19, 2012	**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.			Corresponds to BA
	AB	5,653,972	8/1997	Desai et al.			Corresponds to BA
	AC	4,910,225	3/1990	Ogawa et al.			Corresponds to BB
	AD	5,110,493	5/1992	Cherng-Chyi et al.			Corresponds to BC
	AE	6,383,471	5/2002	Chen et al.			Corresponds to BD
	AF	4,045,576	8/1977	Welstead, Jr. et al.			Corresponds to BF
	AG	4,683,242	7/1987	Poser			Corresponds to BG
	AH	6,319,513	11/2001	Dobrozsi			
	AI	2007/0082857	4/2007	Sawa			

FOREIGN PATENT DOCUMENTS

		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION YES	TRANSLATION NO
	BA	9-503791	4/1997	JP				
	BB	2-124819	5/1990	JP				
	BC	1-104623	4/1989	JP				
	BD	00/59475	10/2000	WO				
/L.S./	BE	11-228404	8/1999	JP			Yes	
/L.S./	BF	5-223052	8/1993	JP			Abstract	
	BG	62-126124	6/1987	JP				No

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.
/L.S./	CB	ISTA Pharmaceuticals, "New Drug Applications: Xibrom", http://www.drugs.com/nda/xibrom_040525.html, accessed online 9/19/2007.
/L.S./	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.

EXAMINER	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.

Sheet 2 of 2

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: January 19, 2012

ATTY DOCKET NO.	**SERIAL NO.**
2012_0088	NEW
APPLICANT	
Shirou SAWA et al.	
FILING DATE	**GROUP**
January 19, 2012	

U.S. PATENT DOCUMENTS

*EXAMINER INITIAL		DOCUMENT NUMBER	DATE	NAME	CLASS	SUBCLASS	FILING DATE IF APPROPRIATE
/L.S./	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			

FOREIGN PATENT DOCUMENTS

		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION YES	TRANSLATION 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							

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

/L.S./	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.
/L.S./	CE	Complete English translation of New Drugs in Japan, 2001, 2001 Edition, Published by Yakuji Nippo Ltd., May 11, 2001, pp. 27-29.
/L.S./	CF	Notice of Opposition dated February 19, 2009 issued by EPO in connection with the corresponding European patent application and Opposition.
/L.S./	CG	http://medical-dictionary.thefreedictionary.com/prophylactic accessed 12/15/2009.

EXAMINER	/Layla Soroush/	DATE CONSIDERED	08/23/2012

*Crossed out references - not provided/no English translation

*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.*

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
13/353,653	01/19/2012	Shirou Sawa	2012_0088

CONFIRMATION NO. 1077

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

PUBLICATION NOTICE

OC000000054205436

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

Publication No.US-2012-0115957-A1
Publication Date:05/10/2012

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

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of	:	Attorney Docket No. 2012_0088
Shirou SAWA et al.	:	**Confirmation No. 1077**
Serial No. 13/353,653	:	Group Art Unit 1627
Filed January 19, 2012	:	Examiner Layla Soroush
AQUEOUS LIQUID PREPARATION CONTAINING 2-AMINO-3-(4-BROMOBENZOYL)PHENYLACETIC ACID	:	**Mail Stop: AMENDMENT**

RESPONSE TO RESTRICTION REQUIREMENT

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

Sir:

Pursuant to the requirement set forth in the Office Action mailed March 16, 2012, Applicants hereby elect invention I, claims 1-2, 4-14, 16 and 19-27.

As the single species, Applicants elect polyethylene glycol fatty acid ester, which is readable on claims 1, 4-5, 7-14, 16, 19-25 and 27.

In view of this election, a full examination on the merits of the present application is respectfully requested.

Respectfully submitted,

Shirou SAWA et al.

By /Warren M. Cheek/

Digitally signed by /Warren M. Cheek/
DN: cn=/Warren M. Cheek/, o, ou, email=wcheek@wenderoth.com, c=US
Date: 2012.04.03 09:42:04 -04'00'

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

WMC/dlk
Washington, D.C. 20005-1503
Telephone (202) 721-8200
Facsimile (202) 721-8250
April 3, 2012

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.

Electronic Acknowledgement Receipt

EFS ID:	12454055
Application Number:	13353653
International Application Number:	
Confirmation Number:	1077
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./pam veazey
Filer Authorized By:	Warren M. Cheek Jr.
Attorney Docket Number:	2012_0088
Receipt Date:	03-APR-2012
Filing Date:	19-JAN-2012
Time Stamp:	14:38:03
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Response to Election / Restriction Filed	AttachA.pdf	189650 a5cc1fb5a5e9267efc3534357cfa42434d5168fd	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:

Total Files Size (in bytes):	189650

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.

UNITED STATES PATENT AND TRADEMARK OFFICE

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

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/353,653	01/19/2012	Shirou Sawa	2012_0088	1077

513 7590 03/16/2012

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	

NOTIFICATION DATE	DELIVERY MODE
03/16/2012	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

ddalecki@wenderoth.com
eoa@wenderoth.com

Office Action Summary	Application No.	Applicant(s)	
	13/353,653	SAWA ET AL.	
	Examiner	Art Unit	
	LAYLA SOROUSH	1627	

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

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *1* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 December 2011*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ 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.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

5)☒ Claim(s) *1,2,4-14 and 16-27* is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☐ Claim(s) _____ is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☒ Claim(s) *1,2,4-14 and 16-27* are subject to restriction and/or election requirement.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

12)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

13)☐ 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:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

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)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Restriction is required under 35 U.S.C. 121 and 372.

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1.

In accordance with 37 CFR 1.499, applicant is required, in reply to this action, to elect a single invention to which the claims must be restricted.

Group I, claim(s) 1-2, 4-14, 16, and 19-27 are drawn to an aqueous liquid preparation.

Group II, claim(s) 17 and 18, drawn to a method for stabilizing 2-amino-3-(4-bromobenzoyl) phenylacetic acid.

2. The inventions listed as Groups I-II do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: the technical feature common to all the claims is the sodium salt/hydrate of 2-amino-3-(4-bromobenzoyl) phenylacetic acid (also known as bromfenac sodium hydrate) in an aqueous liquid preparation. Such a preparation has been disclosed in "New Drugs in Japan, 2001" (translation of table (2), provided by applicant). Therefore, since the technical feature common to the claims was known in the art at the time of the invention, no corresponding special technical feature is present in the claims.

3. This application contains claims directed to more than one species of the generic invention. These species are deemed to lack unity of invention because they are not so linked as to form a single general inventive concept under PCT Rule 13.1.

The species are as follows:

Various alkyl aryl polyether alcohol type polymer or polyethylene glycol fatty acid ester.

Applicant is required, in reply to this action, to elect a single species to which the claims shall be restricted if no generic claim is finally held to be allowable. The reply must also identify the claims readable on the elected species, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered non-responsive unless accompanied by an election.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which are written in dependent form or otherwise include all the limitations of an allowed generic claim as provided by 37 CFR 1.141. If claims are added after the election, applicant must indicate which are readable upon the elected species. MPEP § 809.02(a).

4. The species listed above do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, the species lack the same or corresponding special technical features for the following reasons: the group of polymer additives does not constitute a proper Markush group, different core polymer repeating groups are represented by the different species or possible other choices, each of which consist of a range of polymer compounds with different chemical and physical properties.

5. Applicant is advised that the reply to this requirement to be complete must include (i) an election of a species or invention to be examined even though the requirement be traversed (37 CFR 1.143) and (ii) identification of the claims encompassing the elected invention.

The election of an invention or species may be made with or without traverse. To reserve a right to petition, the election must be made with traverse. If the reply does not distinctly and specifically point out supposed errors in the restriction requirement, the election shall be treated as an election without traverse.

Should applicant traverse on the ground that the inventions or species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the inventions or species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C.103(a) of the other invention.

6. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Election

A telephone call to the attorney is not required where: 1) the restriction requirement is complex, 2) the application is being prosecuted pro se, or 3) the examiner knows from past experience that a telephone election will not be made (MPEP 812.01). Since the restriction election is considered complex, a call to the attorney for a telephone election was not made.

Applicant is advised that the reply to this requirement to be complete must include (i) an election of a species or invention to be examined even though the requirement may be traversed (37 CFR 1.143) and (ii) identification of the claims encompassing the elected invention.

The election of an invention or species may be made with or without traverse. To preserve a right to petition, the election must be made with traverse. If the reply does not distinctly and specifically point out supposed errors in the restriction requirement, the election shall be treated as an election without traverse.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Conclusion

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 Monday through Friday from 8:30 a.m. to 5:00 p.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).

/SREENI PADMANABHAN/

Supervisory Patent Examiner, Art Unit 1627

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of	:	Attorney Docket No. 2012_0088
Shirou SAWA et al.	:	Confirmation No. 1077
Serial No. 13/353,653	:	Group Art Unit 1627
Filed January 19, 2012	:	Examiner Layla Soroush
AQUEOUS LIQUID PREPARATION CONTAINING 2-AMINO-3-(4-BROMOBENZOYL)PHENYLACETIC ACID **(Rule 1.53(b) Divisional of Serial No. 10/525,006, Filed March 28, 2005)**	:	**Mail Stop: Amendment**

SECOND PRELIMINARY AMENDMENT

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

Sir:

Please amend the above-identified application as follows:

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.

REMARKS

The present application is a divisional application of Serial No. 10/525,006. The claims are amended to exclude the subject matter of the allowed parent patent claims. New claims 19-27 are added for additional patent protection.

Favorable action on the merits is solicited.

Respectfully submitted,

Shirou SAWA et al.

By /Warren M. Cheek/

Digitally signed by /Warren M. Cheek/
DN: cn=/Warren M. Cheek/, o, ou, email=wcheek@wenderoth.com, c=US
Date: 2012.02.15 10:34:13 -05'00'

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

WMC/dlk
Washington, D.C. 20005-1503
Telephone (202) 721-8200
Facsimile (202) 721-8250
February 15, 2012

Electronic Patent Application Fee Transmittal

Application Number:	13353653
Filing Date:	19-Jan-2012
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:	2012_0088

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:				
Claims in excess of 20	1202	5	60	300
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
			Total in USD ($)	**300**

Electronic Acknowledgement Receipt

EFS ID:	12081493
Application Number:	13353653
International Application Number:	
Confirmation Number:	1077
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./ann leveille
Filer Authorized By:	Warren M. Cheek Jr.
Attorney Docket Number:	2012_0088
Receipt Date:	15-FEB-2012
Filing Date:	19-JAN-2012
Time Stamp:	14:34:51
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Credit Card
Payment was successfully received in RAM	$300
RAM confirmation Number	807
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		AttachA_Pa.pdf	214214 0cdcc9e77894ff60e39f0529a3fb18cdbb51f13e	yes	6

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Preliminary Amendment	1	1
	Claims	2	5
	Applicant Arguments/Remarks Made in an Amendment	6	6

Warnings:

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Information:

2	Fee Worksheet (SB06)	fee-info.pdf	30927 307724ea2b381e6be97f193f49a6bf9e69a01db3	no	2

Warnings:

Information:

Total Files Size (in bytes):	245141

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.

PTO/SB/06 (07-06)
Approved for use through 1/31/2007. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number	Filing Date	☐ To be Mailed
13/353,653	01/19/2012	

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY RATE ($)	SMALL ENTITY FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY FEE ($)
☒ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	380
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =		OR	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =			X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	380

APPLICATION AS AMENDED – PART II

AMENDMENT 02/15/2012	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE ($)	SMALL ENTITY ADDITIONAL FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	* 25	Minus	** 20	= 5	X $ =		OR	X $60=	300
Independent (37 CFR 1.16(h))	* 4	Minus	***5	= 0	X $ =		OR	X $250=	0
☐ Application Size Fee (37 CFR 1.16(s))									
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
					TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	300

AMENDMENT	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)		RATE ($)	ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =		OR	X $ =	
Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =		OR	X $ =	
☐ Application Size Fee (37 CFR 1.16(s))									
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
					TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".

The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

Legal Instrument Examiner:
/GWENDOLYN MYERS/

Amendments to the Claims

1. (Currently amended) An aqueous liquid preparation comprising 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof, and an alkyl aryl polyether alcohol type polymer or a polyethylene glycol fatty acid ester, provided that the alkyl aryl polyether alcohol type polymer is not tyloxapol.

2. (Original) The aqueous liquid preparation according to claim 1, wherein the alkyl aryl polyether alcohol type polymer has a polymerization degree of 3 to 10, the alkyl contains 1 to 18 carbon atoms, the aryl is a phenyl residue, and the polyether alcohol is represented by the formula $O(CH_2CH_2O)_xH$ in which X is an integer of 5 to 100.

3. (Canceled)

4. (Original) The aqueous liquid preparation according to claim 1, wherein the carbon number of the fatty acid in the polyethylene glycol fatty acid ester is 12 to 18.

5. (Previously presented) The aqueous liquid preparation according to claim 1, wherein the polyethylene glycol fatty acid ester is polyethylene glycol monostearate.

6. (Previously presented) The aqueous liquid preparation according to claim 1, wherein the concentration of the alkyl aryl polyether alcohol type polymer is selected from a range of minimum concentration of 0.01 w/v % to maximum concentration of 0.5 w/v %.

7. (Previously presented) The aqueous liquid preparation according to claim 1, wherein the concentration of the polyethylene glycol fatty acid ester is selected from a range of minimum concentration of 0.02 w/v % to maximum concentration of 0.1 w/v %.

8. (Previously presented) The aqueous liquid preparation according to claim 1, wherein the concentration of the 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof is 0.01 to 0.5 w/v %.

9. (Previously presented) The aqueous liquid preparation according to claim 1, wherein benzalkonium chloride is contained as a preservative.

10. (Previously presented) The aqueous liquid preparation according to claim 1, wherein the pharmacologically acceptable salt of 2-amino-3-(4-bromobenzoyl)phenylacetic acid is a sodium salt.

11. (Previously presented) The aqueous liquid preparation according to claim 1, wherein the pH of the aqueous liquid preparation is within a range of 7 to 9.

12. (Original) The aqueous liquid preparation according to claim 11, wherein the pH of the aqueous liquid preparation is within a range of 7.5 to 8.5.

13. (Previously presented) The aqueous liquid preparation according to claim 1, wherein the aqueous liquid preparation is an eye drop.

14. (Previously presented) The aqueous liquid preparation according to claim 1, wherein the aqueous liquid preparation is a nasal drop.

15. (Canceled)

16. (Original) An eye drop comprising sodium 2-amino-3-(4-bromobenzoyl)phenylacetate hydrate and 0.02 to 0.1 w/v % of polyethylene glycol monostearate.

17. (Original) A method for stabilizing 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof in an aqueous liquid preparation, which comprises incorporating tyloxapol or polyethylene glycol monostearate into an aqueous liquid preparation containing 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof.

18. (Original) A method for inhibiting decrease in preservative effect of a preservative in an aqueous liquid preparation of 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof, which comprises incorporating tyloxapol or polyethylene glycol monostearate into an aqueous liquid preparation containing 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof and a preservative.

19. (New) The aqueous liquid preparation according to claim 1, which consists essentially of the following two components, wherein the first component is the 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof, and the second component is the alkyl aryl polyether alcohol type polymer or the polyethylene glycol fatty acid ester.

20. (New) The aqueous liquid preparation according to claim 1, which is formulated for ophthalmic administration.

21. (New) The aqueous liquid preparation according to claim 1, wherein when a quaternary ammonium compound is included in said liquid preparation, the quaternary ammonium compound is benzalkonium chloride.

22. (New) The aqueous liquid preparation according to claim 1, which further includes one or more additives selected from the group consisting of a preservative, buffer, thickener, stabilizer, chelating agent, and pH controlling agent.

23. (New) The aqueous liquid preparation according to claim 1, wherein said preservative is benzalkonium chloride; wherein said buffer is boric acid and/or sodium borate; wherein said thickener is polyvinylpyrrolidone; wherein said stabilizer is sodium sulfite; wherein said chelating agent is sodium edetate; and wherein said pH controlling agent is sodium hydroxide.

24. (New) The aqueous liquid preparation according to claim 1, wherein the concentration of the 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt is about 0.2 w/v %.

25. (New) The aqueous liquid preparation according to claim 1, wherein the hydrate is at least one selected from a 1/2 hydrate, 1 hydrate and 3/2 hydrate.

26. (New) The aqueous liquid preparation according to claim 1, which contains the alkyl aryl polyether alcohol type polymer and does not contain the polyethylene glycol fatty acid ester.

27. (New) The aqueous liquid preparation according to claim 1, which contains the polyethylene glycol fatty acid ester and does not contain the alkyl aryl polyether alcohol type polymer.

日　本　国　特　許　庁
JAPAN PATENT OFFICE

別紙添付の書類に記載されている事項は下記の出願書類に記載されている事項と同一であることを証明する。

This is to certify that the annexed is a true copy of the following application as filed with this Office.

出　願　年　月　日
Date of Application: ２００３年　１月２１日

出　願　番　号
Application Number: 特願２００３－０１２４２７

パリ条約による外国への出願に用いる優先権の主張の基礎となる出願の国コードと出願番号
The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is ＪＰ２００３－０１２４２７

出　願　人
Applicant(s): 千寿製薬株式会社

２０１２年　２月　６日

特許庁長官
Commissioner,
Japan Patent Office 岩井良行

【書類名】特許願

【整理番号】598-03

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【あて先】特許庁長官　殿

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A61K　9/08

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A61K 47/32

A61P 27/02

A61P 27/16

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【包括委任状番号】0104918

【プルーフの要否】要

【書類名】　　明細書

【発明の名称】　　２－アミノ－３－（４－ブロモベンゾイル）フェニル酢酸含有水性液剤

【特許請求の範囲】

【請求項１】２－アミノ－３－（４－ブロモベンゾイル）フェニル酢酸もしくはその薬理学的に許容できる塩またはそれらの水和物と、アルキルアリールポリエーテルアルコール型ポリマーまたはポリエチレングリコール脂肪酸エステルを含有する水性液剤。

【請求項２】アルキルアリールポリエーテルアルコール型ポリマーはその重合度が３～１０であり、アルキルの炭素数が１～１８であり、アリールがフェノール残基であり、かつポリエーテルアルコールが式（CH_2CH_2O）$_X$Ｈで表され、式中のＸは５～１００の整数を示すものである請求項１記載の水性液剤。

【請求項３】アルキルアリールポリエーテルアルコール型ポリマーがチロキサポールである請求項１または２に記載の水性液剤。

【請求項４】ポリエチレングリコール脂肪酸エステル中の脂肪酸の炭素数が１２～１８である請求項１記載の水性液剤。

【請求項５】ポリエチレングリコール脂肪酸エステルがモノステアリン酸ポリエチレングリコールである請求項１または４に記載の水性液剤。

【請求項６】アルキルアリールポリエーテルアルコール型ポリマーの濃度は下限濃度が０．０１ｗ／ｖ％で、上限濃度が０．５ｗ／ｖ％の範囲から選択される請求項１～３のいずれかに記載の水性液剤。

【請求項７】ポリエチレングリコール脂肪酸エステルの濃度は下限濃度が０．０２ｗ／ｖ％で、上限濃度が０．１ｗ／ｖ％の範囲から選択される請求項１、２または４のいずれかに記載の水性液剤。

【請求項８】２－アミノ－３－（４－ブロモベンゾイル）フェニル酢酸もしくはその薬理学的に許容できる塩またはそれらの水和物の濃度は０．０１～０．５ｗ／ｖ％である請求項１～７のいずれかに記載の水性液剤。

【請求項９】保存剤として塩化ベンザルコニウムを含有する請求項１～８のいずれかに記載の水性液剤。

【請求項１０】２－アミノ－３－（４－ブロモベンゾイル）フェニル酢酸の薬理学的に許容できる塩がナトリウム塩である請求項１～９のいずれかに記載の水性液剤。

【請求項１１】水性液剤のｐＨが７～９の範囲内である請求項１～１０のいずれかに記載の水性液剤。

【請求項１２】水性液剤のｐＨが７．５～８．５の範囲内である請求項１１に記載の水性液剤。

【請求項１３】点眼液である請求項１～１２のいずれかに記載の水性液剤。

【請求項１４】点鼻液である請求項１～１２のいずれかに記載の水性液剤。

【請求項１５】２－アミノ－３－（４－ブロモベンゾイル）フェニル酢酸ナトリウム・水和物およびチロキサポール０．０１ｗ／ｖ％～０．５ｗ／ｖ％を含有する点眼液。

【請求項１６】２－アミノ－３－（４－ブロモベンゾイル）フェニル酢酸ナトリウム・水和物およびモノステアリン酸ポリエチレングリコール０．０２ｗ／ｖ％～０．１ｗ／ｖ％を含有する点眼液。

【請求項１７】２－アミノ－３－（４－ブロモベンゾイル）フェニル酢酸もしくはその薬理学的に許容できる塩またはそれらの水和物を含有する水性液剤にチロキサポールまたはモノステアリン酸ポリエチレングリコールを配合することを特徴とする、水性液剤中の２－アミノ－３－（４－ブロモベンゾイル）フェニル酢酸、その薬理学的に許容できる塩およびそれらの水和物を安定化する方法。

【請求項１８】２－アミノ－３－（４－ブロモベンゾイル）フェニル酢酸もしくはその薬理学的に許容できる塩またはそれらの水和物および保存剤を含有する水性液剤にチロキサポールまたはモノステアリン酸ポリエチレングリコールを配合することを特徴とする、該水性液剤中の保存剤の防腐効力の低下を抑制する方法。

【発明の詳細な説明】

【０００１】

【発明の属する技術分野】

本発明は、２－アミノ－３－（４－ブロモベンゾイル）フェニル酢酸もしくは

その薬理学的に許容できる塩またはそれらの水和物を含有する水性液剤に関する。さらに詳しくは、本発明は、２－アミノ－３－（４－ブロモベンゾイル）フェニル酢酸もしくはその薬理学的に許容できる塩またはそれらの水和物とアルキルアリールポリエーテルアルコール型ポリマーまたはポリエチレングリコール脂肪酸エステルを含有する水性液剤に関する。

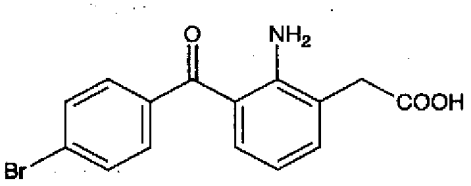
【０００２】

【従来の技術】

次の式（Ｉ）：

【０００３】

【化１】



【０００４】

で表され、化学名が２－アミノ－３－（４－ブロモベンゾイル）フェニル酢酸（一般名：ブロムフェナク）である化合物を包含するベンゾイルフェニル酢酸誘導体が知られている（特許文献１参照。）。２－アミノ－３－（４－ブロモベンゾイル）フェニル酢酸、その薬理学的に許容できる塩およびそれらの水和物は、非ステロイド性抗炎症剤として知られ、眼科領域においては外眼部および前眼部の炎症性疾患（眼瞼炎、結膜炎、強膜炎、術後炎症）に対して有効であり、そのナトリウム塩として点眼液の形態で実用に供されている（非特許文献１参照）。

【０００５】

上記点眼液は、２－アミノ－３－（４－ブロモベンゾイル）フェニル酢酸に、水溶性高分子（ポリビニルピロリドン、ポリビニルアルコールなど）および亜硫酸塩（亜硫酸ナトリウム塩、亜硫酸カリウム塩など）を添加することにより、２－アミノ－３－（４－ブロモベンゾイル）フェニル酢酸の安定化が図られている（特許文献３参照。）。

【０００６】

また上記以外の点眼剤として、酸性眼科用試剤に抗菌性高分子４級アンモニウム化合物およびホウ酸を配合させてなる安定な眼科用組成物が報告され、酸性眼科用試剤の例示として２－アミノ－３－（４－ブロモベンゾイル）フェニル酢酸が挙げられている（特許文献４参照。）。

【特許文献１】

特開昭５２－２３０５２号公開公報

【特許文献２】

特開昭６２－１２６１２４号公開公報

【特許文献３】

特許第２６８３６７６号公報

【特許文献４】

特許第２９５４３５６号公報，６欄，２６－２７行，４５行

【非特許文献１】

「最近の新薬２００１」、２００１年版、株式会社薬事日報社、２００１年５月１１日、ｐ．２７－２９

【０００７】

【発明が解決しようとする課題】

本発明は、２－アミノ－３－（４－ブロモベンゾイル）フェニル酢酸もしくはその薬理学的に許容できる塩またはそれらの水和物を含有する、眼に刺激のないｐＨ領域で安定で、かつ充分な防腐効力を有する水性液剤を提供することにある。

【０００８】

また、本発明の他の目的は、水溶液における２－アミノ－３－（４－ブロモベンゾイル）フェニル酢酸もしくはその薬理学的に許容できる塩またはそれらの水和物の安定化方法を提供することにある。

【０００９】

さらに本発明の他の目的は、２－アミノ－３－（４－ブロモベンゾイル）フェニル酢酸もしくはその薬理学的に許容できる塩またはそれらの水和物および防腐剤を含有する水性液剤中の防腐剤の防腐効力の低下を抑制する方法を提供するこ

とにある。

【００１０】

【課題を解決するための手段】

本発明者らは種々検討を重ねた結果、２－アミノ－３－（４－ブロモベンゾイル）フェニル酢酸、その薬理学的に許容される塩およびそれらの水和物がチロキサポールなどのアルキルアリールポリエーテル型ポリマーまたはモノステアリン酸ポリエチレングリコールなどのポリエチレングリコール脂肪酸エステルを添加することにより、眼刺激のないｐＨ領域において安定で、かつ充分な防腐効力を有することを見出し、さらに研究を進めて本発明を完成させた。

【００１１】

すなわち、本発明は、

（１）２－アミノ－３－（４－ブロモベンゾイル）フェニル酢酸もしくはその薬理学的に許容できる塩またはそれらの水和物と、アルキルアリールポリエーテルアルコール型ポリマーまたはポリエチレングリコール脂肪酸エステルを含有する水性液剤。

（２）アルキルアリールポリエーテルアルコール型ポリマーはその重合度が３～１０であり、アルキルの炭素数が１～１８であり、アリールがフェノール残基であり、かつポリエーテルアルコールが式（$CH_2CH_2O)_XH$で表され、式中のＸは５～１００の整数を示すものである上記（１）記載の水性液剤。

（３）アルキルアリールポリエーテルアルコール型ポリマーがチロキサポールである上記（１）または（２）に記載の水性液剤。

（４）ポリエチレングリコール脂肪酸エステル中の脂肪酸の炭素数が１２～１８である上記（１）記載の水性液剤。

（５）ポリエチレングリコール脂肪酸エステルがモノステアリン酸ポリエチレングリコールである上記（１）または（４）に記載の水性液剤。

（６）アルキルアリールポリエーテルアルコール型ポリマーの濃度は下限濃度が０．０１ｗ／ｖ％で、上限濃度が０．５ｗ／ｖ％の範囲から選択される上記（１）～（３）のいずれかに記載の水性液剤。

（７）ポリエチレングリコール脂肪酸エステルの濃度は下限濃度が０．０２ｗ／

ｖ％で、上限濃度が０．１ｗ／ｖ％の範囲から選択される上記（１）、（２）または（４）のいずれかに記載の水性液剤。

（８）２－アミノ－３－（４－ブロモベンゾイル）フェニル酢酸もしくはその薬理学的に許容できる塩またはそれらの水和物の濃度は０．０１～０．５ｗ／ｖ％である上記（１）～（７）のいずれかに記載の水性液剤。

（９）保存剤として塩化ベンザルコニウムを含有する上記（１）～（８）のいずれかに記載の水性液剤。

（１０）２－アミノ－３－（４－ブロモベンゾイル）フェニル酢酸の薬理学的に許容できる塩がナトリウム塩である上記（１）～（９）のいずれかに記載の水性液剤。

（１１）水性液剤のｐＨが７～９の範囲内である上記（１）～（１０）のいずれかに記載の水性液剤。

（１２）水性液剤のｐＨが７．５～８．５の範囲内である上記（１１）に記載の水性液剤。

（１３）点眼液である上記（１）～（１２）のいずれかに記載の水性液剤。

（１４）点鼻液である上記（１）～（１２）のいずれかに記載の水性液剤。

（１５）２－アミノ－３－（４－ブロモベンゾイル）フェニル酢酸ナトリウム・水和物およびチロキサポール０．０１ｗ／ｖ％～０．５ｗ／ｖ％を含有する点眼液。

（１６）２－アミノ－３－（４－ブロモベンゾイル）フェニル酢酸ナトリウム・水和物およびモノステアリン酸ポリエチレングリコール０．０２ｗ／ｖ％～０．１ｗ／ｖ％を含有する点眼液。

（１７）２－アミノ－３－（４－ブロモベンゾイル）フェニル酢酸もしくはその薬理学的に許容できる塩またはそれらの水和物を含有する水性液剤にチロキサポールまたはモノステアリン酸ポリエチレングリコールを配合することを特徴とする、水性液剤中の２－アミノ－３－（４－ブロモベンゾイル）フェニル酢酸、その薬理学的に許容できる塩およびそれらの水和物を安定化する方法。

（１８）２－アミノ－３－（４－ブロモベンゾイル）フェニル酢酸もしくはその薬理学的に許容できる塩またはそれらの水和物および保存剤を含有する水性液剤

にチロキサポールまたはモノステアリン酸ポリエチレングリコールを配合することを特徴とする、該水性液剤中の保存剤の防腐効力の低下を抑制する方法に関する。

【００１２】

本発明において、２－アミノ－３－（４－ブロモベンゾイル）フェニル酢酸の薬理学的に許容できる塩としては、例えば、ナトリウム塩、カリウム塩などのアルカリ金属塩やカルシウム塩、マグネシウム塩などのアルカリ土類金属塩などが挙げられる。これらの塩のうち、特にナトリウム塩が好ましい。

【００１３】

２－アミノ－３－（４－ブロモベンゾイル）フェニル酢酸およびその薬理学的に許容できる塩は、例えば、特許文献１記載の方法またはそれに準じた方法により適宜製造することができる。これら化合物は、合成の条件、再結晶の条件などによりそれらの水和物として得られる。水和物としては例えば３／２水和物が例示される。

【００１４】

本発明の水性液剤において、２－アミノ－３－（４－ブロモベンゾイル）フェニル酢酸もしくはその薬理学的に許容できる塩またはそれらの水和物の含有量は、通常、０．０１ｗ/ｖ％～０．５ｗ/ｖ％程度、好ましくは０．０５ｗ/ｖ％～０．２ｗ/ｖ％程度、特に好ましくは０．１ｗ/ｖ％程度とし、使用目的、適応症状の程度に応じて適宜増減する。

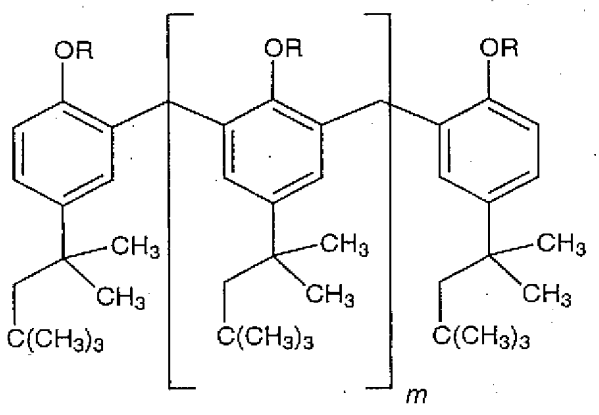
【００１５】

本発明において２－アミノ－３－（４－ブロモベンゾイル）フェニル酢酸もしくはその薬理学的に許容できる塩またはそれらの水和物の安定化剤として用いられる、非イオン性界面活性剤のアルキルアリールポリエーテルアルコール型ポリマー（重合度：３～１０）は、アルキルの炭素数は１～１８程度である。具体的には、たとえばメチル基、エチル基、プロピル基、イソプロピル基、シクロプロピル基、ブチル基、イソブチル基、ｓｅｃ－ブチル基、ｔｅｒｔ－ブチル基、シクロブチル基、ペンチル基、イソペンチル基、ネオペンチル基、ｔｅｒｔ－ペンチル基、１－エチルプロピル基、４－メチルペンチル基、１，１ジメチルブチル

基、２，２－ジメチルブチル基、１，２－ジメチルブチル基、２－エチルブチル基、シクロペンチル基、ヘキシル基、シクロヘキシル基、ヘプチル基、イソヘプチル基、オクチル基、イソオクチル基、ノニル基、イソノニル基、デシル基、イソデシル基、ウンデシル基、イソウンデシル基、ドデシル基、イソドデシル基、トリデシル基、イソトリデシル基、テトラデシル基、イソテトラデシル基、ペンタデシル基、イソペンタデシル基、ヘキサデシル基、イソヘキサデシル基、ヘプタデシル基、イソヘプタデシル基、オクタデシル基、イソオクタデシル基およびそれらの異性体などが挙げられるが、これらのうちオクチル基の異性体である１，１，３，３－テトラメチルブチル基が特に好ましい。上記アリールとしてはフェノール残基が好ましい。上記ポリエーテルアルコールとしては、式（CH_2CH_2O）$_X$Ｈ（式中のＸは５～１００の整数を示す。）で表されるポリエーテルアルコール、好ましくはＸは５～３０の整数であるポリエーテルアルコール、さらに好ましくはＸは８～１０の整数であるポリエーテルアルコールである。上記アルキルアリールポリエーテルアルコール型ポリマーのうち、下記構造を有するチロキサポール（Ｔｙｌｏｘａｐｏｌ）が特に好ましい。

【００１６】

【化２】



$R = (CH_2CH_2O)_xH$

$x = 8 - 10$

$m < 6$

【００１７】

本発明において２－アミノ－３－（４－ブロモベンゾイル）フェニル酢酸もしくはその薬理学的に許容できる塩またはそれらの水和物の安定化剤として用いられる、非イオン性界面活性剤のポリエチレングリコール脂肪酸エステルの脂肪酸は炭素数１２～１８の脂肪酸が好ましい。具体的化合物としては、モノステアリン酸ポリエチレングリコール、モノラウリン酸ポリエチレングリコール、モノオレイン酸ポリエチレングリコール、ジイソステアリン酸ポリエチレングリコール、ジラウリル酸ポリエチレングリコール、ジオレイン酸ポリエチレングリコールなどが挙げられる。これらのうちモノステアリン酸ポリエチレングリコールが好ましく、ステアリン酸ポリオキシル４０（Ｐｏｌｙｏｘｙｌ　４０　ｓｔｅａｒａｔｅ）が特に好ましい。ステアリン酸ポリオキシル４０は、酸化エチレンの縮重合体のモノステアリン酸エステルで、$C_{17}H_{35}COO(CH_2CH_2O)_nH$で表され、ｎは約４０の非イオン性界面活性剤である。

【００１８】

本発明の水性液剤において、アルキルアリールポリエーテルアルコール型ポリマーの含有量は使用する化合物の種類などによって異なるが、下限０．０１ｗ/ｖ％程度、上限０．５ｗ/ｖ％程度である。たとえば、チロキサポールの含有量は、下限０．０１、０．０２、０．０３ｗ/ｖ％程度、上限０．０５、０．１、０．３、０．５ｗ/ｖ％程度、好ましくは下限０．０２ｗ/ｖ％程度、上限０．０５ｗ/ｖ％程度である。

【００１９】

本発明の水性液剤において、ポリエチレングリコール脂肪酸エステルの含有量は使用する化合物の種類などによって異なるが、下限０．０２ｗ/ｖ％程度、上限０．１ｗ/ｖ％程度である。たとえば、モノステアリン酸ポリエチレングリコールの含有量は、下限０．０２ｗ/ｖ％程度、上限０．１ｗ/ｖ％程度、好ましくは下限０．０２ｗ/ｖ％程度、上限０．０５ｗ/ｖ％程度である。

【００２０】

本発明の水性液剤において、たとえばチロキサポールの配合比は、２－アミノ－３－（４－ブロモベンゾイル）フェニル酢酸もしくはその薬理学的に許容できる塩またはそれらの水和物１重量部に対し、下限０．１、０．２重量部程度、上

限０．５、１、３、５重量部程度である。

【００２１】

本発明の水性液剤において、たとえばモノステアリン酸ポリエチレングリコールの配合比は、２－アミノ－３－（４－ブロモベンゾイル）フェニル酢酸もしくはその薬理学的に許容できる塩またはそれらの水和物１重量部に対し、下限０．２重量部程度、上限０．５、１重量部程度である。

【００２２】

本発明の水性液剤に用いられる防腐剤としては、例えば、塩化ベンザルコニウムや塩化ベンゼトニウムなどの第４級アンモニウム塩類、グルコン酸クロルヘキシジンなどが挙げられるが、特に塩化ベンザルコニウムが好ましい。

【００２３】

さらに、本発明の水性液剤には、本発明の目的に反しない限り、通常用いられる等張化剤、緩衝剤、粘稠化剤、安定化剤、キレート剤、ｐＨ調整剤、芳香剤等の各種添加剤を適宜添加してもよい。等張化剤としては、塩化ナトリウム、塩化カリウム、グリセリン、マンニトール、ソルビトール、ホウ酸、ブドウ糖、プロピレングリコールなどが挙げられる。緩衝剤としては、例えば、リン酸緩衝剤、ホウ酸緩衝剤、クエン酸緩衝剤、酒石酸緩衝剤、酢酸緩衝剤、ホウ酸、ホウ砂、アミノ酸などが挙げられる。粘稠化剤としては、ポリビニルピロリドン、カルボキシメチルセルロース、カルボキシプロピルセルロース、ヒドロキシエチルセルロース、ヒドロキシプロピルセルロース、ヒドロキシプロピルメチルセルロース、ポリビニルアルコール、ポリアクリル酸ナトリウムなどが挙げられる。安定化剤としては、亜硫酸ナトリウムなどの亜硫酸塩などが挙げられる。キレート剤としては、エデト酸ナトリウム、クエン酸ナトリウム、縮合燐酸ナトリウムなどが挙げられる。ｐＨ調整剤としては、塩酸、水酸化ナトリウム、リン酸、酢酸などが挙げられる。芳香剤としては、１－メントール、ボルネオール、カンフル、ユーカリ油などが挙げられる。

【００２４】

本発明の水性液剤に配合される上記各添加剤の濃度は、例えば等張化剤は浸透圧比が０．８～１．２程度になる濃度に配合し、緩衝剤は０．０１～２ｗ／ｖ％

程度、粘稠化剤は０．１～１０ｗ／ｖ％程度である。

【００２５】

本発明の水性液剤のｐＨは、約７～９程度、好ましくは約７．５～８．５程度に調整される。

【００２６】

本発明の水性液剤においては、本発明の目的に反しない限り、その他の同種または別種の薬効成分を適宜含有させてもよい。

【００２７】

本発明の水性液剤は、自体公知の調製法、例えば、第１４改正日本薬局方、製剤総則の液剤あるいは点眼剤に記載された方法で製造することができる。

【００２８】

本発明の水性液剤は、温血動物（例えば、ヒト、ラット、マウス、ウサギ、ウシ、ブタ、イヌ、ネコなど）に使用することができる。

【００２９】

本発明の水性液剤を、例えば、点眼剤として使用する場合は、外眼部および前眼部の炎症性疾患、具体的には例えば眼瞼炎、結膜炎、強膜炎、術後炎症などに用いることができる。その投与量は、例えば２－アミノ－３－（４－ブロモベンゾイル）フェニル酢酸ナトリウム・水和物０．１ｗ／ｖ％含有する本発明の点眼剤を成人に点眼する場合は、１回１～２滴を１日３～６回点眼すればよい。なお、適応症状の程度などにより、適宜投与回数を増減する。

【００３０】

【実施例】

以下に、実験例、実施例を挙げて、本発明をさらに詳細に説明するが、本発明はこれらによって限定されるものではない。

【００３１】

実験例１　２－アミノ－３－（４－ブロモベンゾイル）フェニル酢酸ナトリウムの安定性試験

（実験方法）

表１に示す４処方の２－アミノ－３－（４－ブロモベンゾイル）フェニル酢酸

ナトリウム配合の点眼液を調製し、ポリプロピレン容器に充填後、６０℃における安定性について試験した。

【００３２】

【表１】

処方	比較例１	Ａ－01	Ａ－02	Ａ－03
2-ｱﾐﾉ-3-(4-ﾌﾞﾛﾓﾍﾞﾝｿﾞｲﾙ)ﾌｪﾆﾙ酢酸ﾅﾄﾘｳﾑ	0.1ｇ	0.1ｇ	0.1ｇ	0.1ｇ
ﾎｳ酸	1.5ｇ	1.5ｇ	1.5ｇ	1.5ｇ
塩化ﾍﾞﾝｻﾞﾙｺﾆｳﾑ	0.005g	0.005g	0.005g	0.005g
ﾎﾟﾘｿﾙﾍﾞｰﾄ80	0.15g	－	－	－
ｽﾃｱﾘﾝ酸ﾎﾟﾘｵｷｼﾙ40	－	0.15g	－	－
ﾁﾛｷｻﾎﾟｰﾙ	－	－	0.15g	0.02g
滅菌精製水	適量	適量	適量	適量
全量	100 mL	100 mL	100 mL	100 mL
ｐＨ	7.0	7.0	7.0	7.0
６０℃－４Ｗ	51.3	63.7	73.8	89.6

【００３３】

表１の残存率（％）は、２－アミノ－３－（４－ブロモベンゾイル）フェニル酢酸ナトリウムの含量に対し、容器からの水分の飛散を補正した値である。表１から明らかなように、ｐＨ７．０、６０℃、４週において、ポリソルベート８０、ステアリン酸ポリオキシル４０、チロキサポール配合点眼液の順で２－アミノ－３－（４－ブロモベンゾイル）フェニル酢酸ナトリウムは安定であった。

また、チロキサポール配合点眼液において、チロキサポール０．０２ｗ／ｖ％の方が０．１５ｗ／ｖ％配合したものよりも２－アミノ－３－（４－ブロモベンゾイル）フェニル酢酸ナトリウムは安定であった。

【００３４】

実験例２　２－アミノ－３－（４－ブロモベンゾイル）フェニル酢酸ナトリウムの安定性試験

（実験方法）

表２に示す５処方の２－アミノ－３－（４－ブロモベンゾイル）フェニル酢酸配合の点眼液を調製し、ポリプロピレン容器に充填した。６０℃、４週間保存後、点眼液中の２－アミノ－３－（４－ブロモベンゾイル）フェニル酢酸量および

点眼液のｐＨを測定した。調整時の２－アミノ－３－（４－ブロモベンゾイル）フェニル酢酸を１００％としたときの残存量およびｐＨを表２に示した。なお残存量は容器からの水分の飛散を補正した値である。

【００３５】

【表２】

処方		A－04	A－05	A－06	A－07	A－08
2-ｱﾐﾉ-3-(4-ﾌﾞﾛﾓﾍﾞﾝｿﾞｲﾙ)ﾌｪﾆﾙ酢酸ﾅﾄﾘｳﾑ		0.1 g	0.1 g	0.1 g	0.1 g	0.1 g
ﾎｳ酸		1.1 g	1.1 g	1.1 g	1.1 g	1.1 g
ﾎｳ砂		1.1 g	1.1 g	1.1 g	1.1 g	1.1 g
塩化ﾍﾞﾝｻﾞﾙｺﾆｳﾑ		0.005g	0.005g	0.005g	0.005g	0.005g
ﾎﾟﾘｿﾙﾍﾞｰﾄ80		－	－	－	－	－
ﾁﾛｷｻﾎﾟｰﾙ		0.02 g	0.05 g	0.03 g	－	－
ｽﾃｱﾘﾝ酸ﾎﾟﾘｵｷｼﾙ40		－	－	－	0.02 g	0.05 g
ﾎﾟﾘﾋﾞﾆﾙﾋﾟﾛﾘﾄﾞﾝ(K-30)		2.0 g	2.0 g	2.0 g	2.0 g	1.0 g
ｴﾃﾞﾄ酸ﾅﾄﾘｳﾑ		0.02 g	0.02 g	0.02 g	0.02 g	0.02 g
水酸化ﾅﾄﾘｳﾑ		適量	適量	適量	適量	適量
滅菌精製水		適量	適量	適量	適量	適量
全量		100 mL	100 mL	100 mL	100 mL	100 mL
ｐＨ		8.17	8.16	8.15	8.19	8.19
60℃－4W	残存量	92.6	90.9	92.0	93.4	93.1
	ｐＨ	8.15	8.16	8.15	8.13	8.14

【００３６】

表２から明らかなように、０．０２、０．０３および０．０５ｗ／ｖ％チロキサポールまたは０．０２、０．０５ｗ／ｖ％ステアリン酸ポリオキシル４０を配合した処方は６０℃、４週で残存率が９０％以上であり、点眼液剤として充分な安定性を示した。

【００３７】

実験例３　２－アミノ－３－（４－ブロモベンゾイル）フェニル酢酸ナトリウム含有水性液剤の防腐効力試験

実験例２のＡ－０４、Ａ－０５およびＡ－０７の処方の防腐効力につき試験した。

その結果を表３に示す。

【００３８】

【表３】

表３－１

A－04	接種菌数	6th	24th	1W	2W	3W	4W
S. aureus	2.1×10^6	3.0×10^1	0	0	0	0	0
E. coli	6.5×10^6	0	0	0	0	0	0
P. aeruginosa	5.8×10^6	0	0	0	0	0	0
C. albicans	3.2×10^5	—	—	0	0	0	0
A. niger	1.8×10^5	—	—	0	0	0	0

Unit : CFU/mL

表３－２

A－05	接種菌数	6th	24th	1W	2W	3W	4W
S. aureus	2.1×10^6	1.7×10^5	2.0×10^1	0	0	0	0
E. coli	6.5×10^6	0	0	0	0	0	0
P. aeruginosa	5.8×10^6	0	0	0	0	0	0
C. albicans	3.2×10^5	—	—	0	0	0	0
A. niger	1.8×10^5	—	—	0	0	0	0

Unit : CFU/mL

表３－３

A－07	接種菌数	6th	24th	1W	2W	3W	4W
S. aureus	2.7×10^6	3.1×10^4	0	0	0	0	0
E. coli	7.4×10^6	0	0	0	0	0	0
P. aeruginosa	8.8×10^6	0	0	0	0	0	0
C. albicans	4.6×10^5	—	—	0	0	0	0
A. niger	1.0×10^5	—	—	0	0	0	0

Unit : CFU/mL

【００３９】

表３－１、表３－２および表３－３から明らかなように、処方Ａ－０４の防腐効力はＥＰ－Ａの基準１）、処方Ａ－０５およびＡ－０７の防腐効力はＥＰ－Ｂの基準２）に適合することがわかった。

【００４０】

１）EP（European　Pharmacopoeia）―Aの基準

細菌（S. aureus, P. aeruginosa）の生菌数が、接種６時間後に１/100以下、２４時間後に1/1000以下となり、２８日後に生菌が検出されないこと。

真菌（C. Albicans,　A. niger）の生菌数が、接種７日後に１/100以下、以降は７日後と同レベルかそれ以下となること。

２）EP―Bの基準

細菌（S. aureus, P. aeruginosa）の生菌数が、接種２４時間後に１/10以下、７日後に1/1000以下となり、以降は７日後と同レベルかそれ以下となること。

真菌（C. Albicans,　A. niger）の生菌数が、接種１４日後に１/10以下、以降は７日後と同レベルかそれ以下となること。

【００４１】

実施例１　点眼液

２－アミノ－３－（４－ブロモベンゾイル）フェニル酢酸ナトリウム・３／２水和物　0.1 g

ホウ酸　1.1 g

ホウ砂　1.1g

塩化ベンザルコニウム　0.005 g

チロキサポール　0.02g

ポリビニルピロリドン（Ｋ－３０）　2.0g

エデト酸ナトリウム　0.02g

水酸化ナトリウム　適量

滅菌精製水　全量100 mL

pH8.17

以上の成分を用いて、常法により点眼液とする。

【００４２】

実施例２　点眼液

２－アミノ－３－（４－ブロモベンゾイル）フェニル酢酸ナトリウム・３／２水和物

	0.1 g
ホウ酸	1.1 g
ホウ砂	1.1g
塩化ベンザルコニウム	0.005 g
チロキサポール	0.05g
ポリビニルピロリドン（Ｋ－３０）	2.0g
エデト酸ナトリウム	0.02g
水酸化ナトリウム	適量
滅菌精製水	全量100 mL
	pH8.16

以上の成分を用いて、常法により点眼液とする。

【００４３】

実施例３　点眼液

２－アミノ－３－（４－ブロモベンゾイル）フェニル酢酸ナトリウム・３／２水和物

	0.1 g
ホウ酸	1.1 g
ホウ砂	1.1g
塩化ベンザルコニウム	0.005 g
ステアリン酸ポリオキシル４０	0.02g
ポリビニルピロリドン（Ｋ－３０）	2.0g
エデト酸ナトリウム	0.02g
水酸化ナトリウム	適量
滅菌精製水	全量100 mL
	pH8.19

以上の成分を用いて、常法により点眼液とする。

【００４４】

【発明の効果】

本発明によれば、２－アミノ－３－（４－ブロモベンゾイル）フェニル酢酸も

しくはその薬理学的に許容できる塩またはそれらの水和物を含有する水性液剤に、チロキサポールなどのアルキルアリールポリエーテルアルコール型ポリマーまたはモノステアリン酸ポリエチレングリコールなどのポリエチレングリコール脂肪酸エステルを配合することにより、２－アミノ－３－（４－ブロモベンゾイル）フェニル酢酸もしくはその薬理学的に許容できる塩またはそれらの水和物を含有する安定な水性液剤を調製できる。また、本発明の水性液剤は充分な防腐効力も有している。

したがって、本発明の水性液剤は、例えば点眼液として、眼瞼炎、結膜炎、強膜炎、術後炎症などの治療に有利に用いられる。

【書類名】　　要約書

【要約】

【課題】安定化された２－アミノ－３－（４－ブロモベンゾイル）フェニル酢酸もしくはその薬理学的に許容できる塩またはそれらの水和物を含有する安定かつ充分な防腐効力を有する水性液剤を提供する。

【解決手段】２－アミノ－３－（４－ブロモベンゾイル）フェニル酢酸もしくはその薬理学的に許容できる塩またはそれらの水和物とチロキサポールなどのアルキルアリールポリエーテルアルコール型ポリマーまたはモノステアリン酸グリコールなどのポリエチレングリコール脂肪酸エステルとを含有する水性液剤。

【選択図】なし

出願人履歴

０００１９９１７５

19900822

新規登録

大阪府大阪市中央区平野町２丁目５番８号

千寿製薬株式会社

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number: 13/353,653

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY FEE($)
BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	380
SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	620
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	250
TOTAL CLAIMS (37 CFR 1.16(i))	18 minus 20 =	*			OR	x 60 =	0.00
INDEPENDENT CLAIMS (37 CFR 1.16(h))	5 minus 3 =	* 2				x 250 =	500
APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						0.00
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							0.00
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	1750

APPLICATION AS AMENDED - PART II

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY ADDITIONAL FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE($)
AMENDMENT A	Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY ADDITIONAL FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE($)
AMENDMENT B	Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".

The "Highest Number Previously Paid For" (Total or Independent) is the highest found in the appropriate box in column 1.

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APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
13/353,653	01/19/2012	1621	1750	2012_0088	18	5

CONFIRMATION NO. 1077

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

FILING RECEIPT

OC000000052306264

Date Mailed: 02/03/2012

Receipt is acknowledged of this non-provisional patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please submit a written request for a Filing Receipt Correction. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections**

Applicant(s)

Shirou Sawa, Kobe-shi, JAPAN;
Shuhei Fujita, Kakogawa, JAPAN;

Power of Attorney: The patent practitioners associated with Customer Number 000513

Domestic Priority data as claimed by applicant

This application is a DIV of 10/525,006 03/28/2005
which is a 371 of PCT/JP2004/000350 01/16/2004

Foreign Applications (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see http://www.uspto.gov for more information.)
JAPAN 2003-012427 01/21/2003

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The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 13/353,653**

Projected Publication Date: 05/10/2012

Non-Publication Request: No

Early Publication Request: No

Title

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

Preliminary Class

562

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of	:	
Shirou SAWA et al.	:	
Serial No. NEW	:	
Filed January 19, 2012	:	
AQUEOUS LIQUID PREPARATION CONTAINING 2-AMINO-3-(4-BROMOBENZOYL)PHENYLACETIC ACID **(Rule 1.53(b) Divisional of Serial No. 10/525,006, Filed March 28, 2005)**	:	Attorney Docket No. 2012_0088

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

Sir:

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

It is requested that the Examiner consider all the information of record in the prior parent application(s) (Serial No. 10/525,006), relied on by the present application under 35 U.S.C. § 120. A copy of any listed reference that was previously cited by or submitted to the PTO in the prior parent application(s) is not required or provided herein (see 37 C.F.R. 1.98(d)).

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,

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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.

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 specified in 37 CFR 1.17(p) is enclosed.

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the certification of paragraph 2 below is provided, and
the fee of $180.00 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.

Respectfully submitted,

Shirou SAWA et al.

/Warren M. Cheek/

Digitally signed by /Warren M. Cheek/
DN: cn=/Warren M. Cheek/, o, ou, email=wcheek@wenderoth.com, c=US
Date: 2012.01.19 13:12:48 -05'00'

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January 19, 2012

Sheet 1 of 2

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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: January 19, 2012

ATTY DOCKET NO.	**SERIAL NO.**
2012_0088	NEW
APPLICANT	
Shirou SAWA et al.	
FILING DATE	**GROUP**
January 19, 2012	

U.S. PATENT DOCUMENTS

*EXAMINER INITIAL		DOCUMENT NUMBER	DATE	NAME	CLASS	SUBCLASS	FILING DATE IF APPROPRIATE
	AA	5,603,929	2/1997	Desai et al.			Corresponds to BA
	AB	5,653,972	8/1997	Desai et al.			Corresponds to BA
	AC	4,910,225	3/1990	Ogawa et al.			Corresponds to BB
	AD	5,110,493	5/1992	Cherng-Chyi et al.			Corresponds to BC
	AE	6,383,471	5/2002	Chen et al.			Corresponds to BD
	AF	4,045,576	8/1977	Welstead, Jr. et al.			Corresponds to BF
	AG	4,683,242	7/1987	Poser			Corresponds to BG
	AH	6,319,513	11/2001	Dobrozsi			
	AI	2007/0082857	4/2007	Sawa			

FOREIGN PATENT DOCUMENTS

		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION YES	TRANSLATION NO
	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

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

	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.
	CB	ISTA Pharmaceuticals, "New Drug Applications: Xibrom", http://www.drugs.com/nda/xibrom_040525.html, 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.

EXAMINER	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.*

Sheet 2 of 2				**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: January 19, 2012				**ATTY DOCKET NO.** 2012_0088		**SERIAL NO.** NEW	
				APPLICANT Shirou SAWA et al.			
				FILING DATE January 19, 2012		**GROUP**	
U.S. PATENT DOCUMENTS							
*EXAMINER INITIAL		DOCUMENT NUMBER	DATE	NAME	CLASS	SUBCLASS	FILING DATE IF APPROPRIATE
	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			

FOREIGN PATENT DOCUMENTS								
		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION YES	TRANSLATION 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							

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

EXAMINER	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.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of	:	
Shirou SAWA et al.	:	
Serial No. NEW	:	
Filed January 19, 2012	:	
AQUEOUS LIQUID PREPARATION CONTAINING 2-AMINO-3-(4-BROMOBENZOYL)PHENYLACETIC ACID **(Rule 1.53(b) Divisional of Serial No. 10/525,006, Filed March 28, 2005)**	:	Attorney Docket No. 2012_0088

PRELIMINARY AMENDMENT

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

Sir:

Prior to calculating the filing fee, please amend the above-identified application as follows:

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.

Amendments to the Specification

Page 1, immediately after the title, please insert the paragraph as follows:

This is a divisional of Serial No. 10/525,006, filed March 28, 2005, which is a U.S. national stage of International Application No. PCT/JP2004/000350 filed January 16, 2004.

Amendments to the Claims

1. (Original) An aqueous liquid preparation comprising 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof, and an alkyl aryl polyether alcohol type polymer or a polyethylene glycol fatty acid ester.

2. (Original) The aqueous liquid preparation according to claim 1, wherein the alkyl aryl polyether alcohol type polymer has a polymerization degree of 3 to 10, the alkyl contains 1 to 18 carbon atoms, the aryl is a phenyl residue, and the polyether alcohol is represented by the formula $O(CH_2CH_2O)_xH$ in which X is an integer of 5 to 100.

3. (Currently amended) The aqueous liquid preparation according to claim 1 ~~or 2~~, wherein the alkyl aryl polyether alcohol type polymer is tyloxapol.

4. (Original) The aqueous liquid preparation according to claim 1, wherein the carbon number of the fatty acid in the polyethylene glycol fatty acid ester is 12 to 18.

5. (Currently amended) The aqueous liquid preparation according to claim 1 ~~or 4~~, wherein the polyethylene glycol fatty acid ester is polyethylene glycol monostearate.

6. (Currently amended) The aqueous liquid preparation according to ~~any one of claims 1 to 3~~ claim 1, wherein the concentration of the alkyl aryl polyether alcohol type polymer is selected from a range of minimum concentration of 0.01 w/v % to maximum concentration of 0.5 w/v %.

7. (Currently amended) The aqueous liquid preparation according to ~~any one of claims 1, 2 or 4~~ claim 1, wherein the concentration of the polyethylene glycol fatty acid ester is selected from a range of minimum concentration of 0.02 w/v % to maximum concentration of 0.1 w/v %.

8. (Currently amended) The aqueous liquid preparation according to ~~any one of claims 1 to 7~~ claim 1, wherein the concentration of the 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof is 0.01 to 0.5 w/v %.

9. (Currently amended) The aqueous liquid preparation according to ~~any one of claims 1 to 8~~ claim 1, wherein benzalkonium chloride is contained as a preservative.

10. (Currently amended) The aqueous liquid preparation according to ~~any one of 1 to 9~~ claim 1, wherein the pharmacologically acceptable salt of 2-amino-3-(4-bromobenzoyl)phenylacetic acid is a sodium salt.

11. (Currently amended) The aqueous liquid preparation according to ~~any one of claims 1 to 10~~ claim 1, wherein the pH of the aqueous liquid preparation is within a range of 7 to 9.

12. (Original) The aqueous liquid preparation according to claim 11, wherein the pH of the aqueous liquid preparation is within a range of 7.5 to 8.5.

13. (Currently amended) The aqueous liquid preparation according to ~~any one of claims 1 to 12~~ claim 1, wherein the aqueous liquid preparation is an eye drop.

14. (Currently amended) The aqueous liquid preparation according to ~~any one of claims 1 to 12~~ claim 1, wherein the aqueous liquid preparation is a nasal drop.

15. (Original) An eye drop comprising sodium 2-amino-3-(4-bromobenzoyl)phenylacetate hydrate and 0.01 to 0.5 w/v % of tyloxapol.

16. (Original) An eye drop comprising sodium 2-amino-3-(4-bromobenzoyl)phenylacetate hydrate and 0.02 to 0.1 w/v % of polyethylene glycol monostearate.

17. (Original) A method for stabilizing 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof in an aqueous liquid preparation,

which comprises incorporating tyloxapol or polyethylene glycol monostearate into an aqueous liquid preparation containing 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof.

18. (Original) A method for inhibiting decrease in preservative effect of a preservative in an aqueous liquid preparation of 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof, which comprises incorporating tyloxapol or polyethylene glycol monostearate into an aqueous liquid preparation containing 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof and a preservative.

REMARKS

The present application is a divisional application of Serial No. 10/525,006 and is directed to original claims 1-18.

Favorable action on the merits is solicited.

Respectfully submitted,

Shirou SAWA et al.

By /Warren M. Cheek/

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Date: 2012.01.19 13:13:11 -05'00'

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January 19, 2012

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of :

Shirou SAWA et al. :

Serial No. NEW :

Filed January 19, 2012 : Attorney Docket No. 2012_0088

AQUEOUS LIQUID PREPARATION CONTAINING 2-AMINO-3-(4-BROMOBENZOYL)PHENYLACETIC ACID
(Rule 1.53(b) Divisional of Serial No. 10/525,006, Filed March 28, 2005)

CLAIM OF PRIORITY UNDER 35 USC 119

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

Sir:

Applicants in the above-identified application hereby claim the date of priority under the International Convention of Japanese Patent Application No. 2003-012427, filed January 21, 2003, as acknowledged in the Declaration of this application.

A certified copy of said Japanese Patent Application is of record in parent application Serial No. 10/525,006, filed March 28, 2005.

Respectfully submitted,

Shirou SAWA et al.

By /Warren M. Cheek/
Digitally signed by /Warren M. Cheek/
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Date: 2012.01.19 13:13:27 -05'00'

Warren M. Cheek
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January 19, 2012

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.

Electronic Patent Application Fee Transmittal

Application Number:	
Filing Date:	
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:	2012_0088

Filed as Large Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Utility application filing	1011	1	380	380
Utility Search Fee	1111	1	620	620
Utility Examination Fee	1311	1	250	250
Pages:				
Claims:				
Independent claims in excess of 3	1201	2	250	500
Miscellaneous-Filing:				
Petition:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Miscellaneous:				
		Total in USD ($)		**1750**

Electronic Acknowledgement Receipt

EFS ID:	11872450
Application Number:	13353653
International Application Number:	
Confirmation Number:	1077
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./pam veazey
Filer Authorized By:	Warren M. Cheek Jr.
Attorney Docket Number:	2012_0088
Receipt Date:	19-JAN-2012
Filing Date:	
Time Stamp:	14:27:00
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Credit Card
Payment was successfully received in RAM	$1750
RAM confirmation Number	831
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	Transmittal of New Application	AttachA_Trans.pdf	240518 facd958da4758a0b5383044112366009c181c247	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		AttachB_Spec.PDF	956107 f3af8d5934c2c9b6160d4dda0bb820a1a16c0dd6	yes	29

Multipart Description/PDF files in .zip description

Document Description	Start	End
Specification	1	24
Claims	25	28
Abstract	29	29

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	Oath or Declaration filed	AttachC_Decl.PDF	162999 a14efe3bc1715c5bd39f59723543407455df74a5	no	3

Warnings:

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Information:

4	Information Disclosure Statement (IDS) Form (SB08)	AttachD1_Ids.pdf	369512 f5c8a09117d8b0c9ce5814c3fe3e69c1252f8472	no	5

Warnings:

Information:

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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.

5		AttachE_Pa.pdf	211729 b43fa96dc4dbf67762470db557e892d0f032355e	yes	6

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Preliminary Amendment	1	1
	Specification	2	2
	Claims	3	5
	Applicant Arguments/Remarks Made in an Amendment	6	6

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	Miscellaneous Incoming Letter	AttachF.pdf	193272 28b8bfe1d8722c43eb325ba9512c487318571999	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:

7	Fee Worksheet (SB06)	fee-info.pdf	37035 30cef0d0640f3082d6f032f217eb03cb4f6e5a07	no	2

Warnings:

Information:

Total Files Size (in bytes):	2171172

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.

Electronic Acknowledgement Receipt

EFS ID:	11872450
Application Number:	13353653
International Application Number:	
Confirmation Number:	1077
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./pam veazey
Filer Authorized By:	Warren M. Cheek Jr.
Attorney Docket Number:	2012_0088
Receipt Date:	19-JAN-2012
Filing Date:	
Time Stamp:	14:27:00
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Credit Card
Payment was successfully received in RAM	$1750
RAM confirmation Number	831
Deposit Account	230975
Authorized User	CHEEK JR.,WARREN M.

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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	Transmittal of New Application	AttachA_Trans.pdf	240518 facd958da4758a0b5383044112366009c181c247	no	1

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Information:

2		AttachB_Spec.PDF	956107 f3af8d5934c2c9b6160d4dda0bb820a1a16c0dd6	yes	29

Multipart Description/PDF files in .zip description

Document Description	Start	End
Specification	1	24
Claims	25	28
Abstract	29	29

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Information:

3	Oath or Declaration filed	AttachC_Decl.PDF	162999 a14efe3bc1715c5bd39f59723543407455df74a5	no	3

Warnings:

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Information:

4	Information Disclosure Statement (IDS) Form (SB08)	AttachD1_Ids.pdf	369512 f5c8a09117d8b0c9ce5814c3fe3e69c1252f8472	no	5

Warnings:

Information:

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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.

5		AttachE_Pa.pdf	211729 b43fa96dc4dbf67762470db557e892d0f032355e	yes	6

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Preliminary Amendment	1	1
	Specification	2	2
	Claims	3	5
	Applicant Arguments/Remarks Made in an Amendment	6	6

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Information:

6	Miscellaneous Incoming Letter	AttachF.pdf	193272 28b8bfe1d8722c43eb325ba9512c487318571999	no	1

Warnings:

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Information:

7	Fee Worksheet (SB06)	fee-info.pdf	37035 30cef0d0640f3082d6f032f217eb03cb4f6e5a07	no	2

Warnings:

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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.

UTILITY
PATENT APPLICATION
TRANSMITTAL
(Only for new nonprovisional applications under 37 CFR 1.53(b)

Attorney Docket No.: 2012_0088

First Named Inventor: Shirou SAWA et al.

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

Express Mail Label No.:

APPLICATION ELEMENTS
See MPEP chapter 600 concerning utility patent application contents.

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

1. [] Fee Transmittal Form

2. [] Small Entity Status is hereby asserted.

3. [X] Specification *[Total Pages: 29]*
Both the claims and abstract must start on a new page
(For information on the preferred arrangement, see MPEP 608.01(a))

4. [] Drawing(s) *(35 USC 113)* *[Total Sheets:]*

5. [X] Oath or Declaration *[Total Pages: 3]*
a.1. [] Newly executed (original or copy)
a.2. [] Unexecuted
b. [X] Copy from a prior application (37 CFR 1.63(d))
(for continuation/divisional with Box 18 completed)
i. [] DELETION OF INVENTOR(S)
Signed statement attached deleting inventor(s) named in the prior application, see 37 CFR 1.63(d)(2) and 1.33(b).

6. [] Application Data Sheet (see 37 CFR 1.76)

7. [] CD-ROM or CD-R in duplicate, large table or computer program *(Appendix)*

8. [] Nucleotide and/or Amino Acid Sequence Submission
(if applicable, all necessary)
a. [] Computer Readable Form
b. Specification Sequence Listing on:
i. [] CD-ROM or CD-R (2 copies); or
ii. [] Paper
c. [] The paper and computer readable copies are identical

ACCOMPANYING APPLICATION PARTS

9. [] Assignment Papers (cover sheet & document(s))
Name of Assignee:
SENJU PHARMACEUTICAL CO., LTD.

10. [] 37 CFR 3.73(b) Statement
(*when there is an assignee*)
[] Power of Attorney

11. [] English Translation Document
(if applicable)

12. [X] Information Disclosure Statement (IDS)/PTO-SB/08
[] Copies of IDS Citations

13. [X] Preliminary Amendment

14. [] Return Receipt Postcard (MPEP 503)
(Should be specifically itemized)

15. [] Certified Copy of Priority Document(s)
(if foreign priority is claimed)

16. [] Non-Publication Request and Certification under 35 U.S.C. 122 (b)(2)(B)(i).
Applicant must attach form PTO/SB/35 or its equivalent.

17. [X] Other - Claim of Priority

18. If a CONTINUING APPLICATION, *check appropriate box, and supply the requisite information below, and in a preliminary amendment, or in an Application Data Sheet :*

[] Continuation [X] Divisional [] Continuation-in-part (CIP) of prior application No. 10/525,006

Prior Application Information: Examiner: Layla Soroush Group Art Unit: 1627

For CONTINUATION OR DIVISIONAL APPS only: The entire disclosure of the prior application, from which an oath or declaration is supplied under Box 5b, is considered a part of the disclosure of the accompanying continuation or divisional application and is hereby incorporated by reference therein. The incorporation can only be relied upon when a portion has been inadvertently omitted from the submitted application parts.

19. CORRESPONDENCE ADDRESS

CUSTOMER NO.

00513

By: /Warren M. Cheek/ Digitally signed by /Warren M. Cheek/ DN: cn=/Warren M. Cheek/, o, ou, email=wcheek@wenderoth.com, c=US Date: 2012.01.19 13:11:33 -05'00'

Warren M. Cheek
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January 19, 2012

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 and for the entire pendency of the present application to Deposit Account No. 23-0975, except fees for multiple dependent claims.

DESCRIPTION

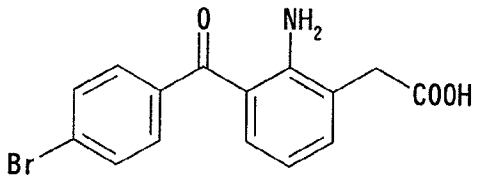
AQUEOUS LIQUID PREPARATION CONTAINING 2-AMINO-3-(4-BROMOBENZOYL)PHENYLACETIC ACID

TECHNICAL FIELD

The present invention relates to an aqueous liquid preparation containing 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof. More particularly, the present invention relates to an aqueous liquid preparation containing 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof and an alkyl aryl polyether alcohol type polymer or a polyethylene glycol fatty acid ester.

BACKGROUND ART

Benzoylphenylacetic acid derivatives including bromfenac (generic name) of formula (I):



of which chemical name is 2-amino-3-(4-bromobenzoyl)phenylacetic acid are known as disclosed in JP-A-23052/1977 and its corresponding US patent No. 4.045,576. 2-Amino-3-(4-bromobenzoyl)phenylacetic acid, its pharmacologically acceptable salt and a hydrate thereof are

known as a non-steroidal anti-inflammatory agent, and they are effective against inflammatory diseases of anterior or posterior segment of the eye, such as blepharitis, conjunctivitis, scleritis, and postoperative inflammation in the field of ophthalmology, and its sodium salt has been practically used in the form of eye drops ("New Drugs in Japan, 2001", 2001 Edition, Published by Yakuji Nippo Ltd., May 11, 2001, p.27-29).

The eye drop as mentioned above is designed to stabilize 2-amino-3-(4-bromobenzoyl)phenylacetic acid by means of addition of a water-soluble polymer (e.g. polyvinylpyrrolidone, polyvinyl alcohol, etc.) and a sulfite (e.g. sodium sulfite, potassium sulfite, etc.)(Japanese patent No. 2,683,676 and its corresponding US patent No.4,910,225).

In addition, as an eye drop other than the above-mentioned one, Japanese patent No. 2,954,356 (corresponding to US patents Nos. 5,603,929 and 5,653,972) discloses a stable ophthalmic composition which comprises incorporating an antibacterial quaternary ammonium polymer and boric acid into an acidic ophthalmic agent. The acidic agent described therein includes, for example, 2-amino-3-(4-bromobenzoyl)phenylacetic acid.

Further, in Japanese patent No. 2,954,356, there is the following description-"Benzalkonium chloride is a widely used preservative in ophthalmic solutions. However, benzalkonium chloride and other quaternary ammonium compounds are generally considered to be incompatible with ophthalmic compositions of drugs with acidic groups, such as nonsteroidal anti-inflammatory drugs. These preservatives lose their

ability to function as they form complexes with the charged drug compounds".

In these prior art references, there is no disclosure that alkyl aryl polyether alcohol type polymers or polyethylene glycol fatty acid esters are able to stabilize an aqueous liquid preparation of 2-amino-3-(4-bromobenzoyl)phenylacetic acid or its pharmacologically acceptable salt, and inhibit decrease in preservative effect of benzalkonium chloride and other quaternary ammonium compounds.

DISCLOSURE OF THE INVENTION

It is an object of the present invention to provide an aqueous liquid preparation comprising 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof, which is stable within a pH range giving no irritation to eyes and in which, when a preservative such as benzalkonium chloride is incorporated therein, preservative effect of the preservative does not substantially deteriorate.

Another object of the invention is to provide a method for stabilizing an aqueous liquid preparation of 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof.

Further object of the invention is to provide an aqueous liquid preparation comprising 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof and a preservative, wherein, when specifically a quaternary ammonium salt such as

benzalkonium chloride is incorporated as a preservative, decrease in preservative effect of said preservative is inhibited.

As a result of various studies, the inventors of the present invention have found that, by adding, for example, an alkyl aryl polyether alcohol type polymer such as tyloxapol, or a polyethylene glycol fatty acid ester such as polyethylene glycol monostearate to an aqueous liquid preparation of 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof, the aqueous solution becomes stable within a pH range giving no irritation to eyes, and change of the 2-amino-3-(4-bromobenzoyl)phenylacetic acid over time can be inhibited, and furthermore, when the aqueous solution contains a preservative, deterioration in the preservative effect of said preservative can be inhibited for a long period of time. The inventors of the present invention have further studied extensively and completed the present invention.

Namely, the present invention relates to:

(1) An aqueous liquid preparation comprising 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof, and an alkyl aryl polyether alcohol type polymer or a polyethylene glycol fatty acid ester,

(2) The aqueous liquid preparation according to the above (1), wherein the alkyl aryl polyether alcohol type polymer has a polymerization degree of 3 to 10, the alkyl contains 1 to 18 carbon atoms, the aryl is a phenyl residue, and the polyether

alcohol is represented by the formula $O(CH_2CH_2O)_xH$ in which X is an integer of 5 to 100,

(3) The aqueous liquid preparation according to the above (1) or (2), wherein the alkyl aryl polyether alcohol type polymer is tyloxapol,

(4) The aqueous liquid preparation according to the above (1), wherein the carbon number of the fatty acid in the polyethylene glycol fatty acid ester is 12 to 18,

(5) The aqueous liquid preparation according to the above (1) or (4), wherein the polyethylene glycol fatty acid ester is polyethylene glycol monostearate,

(6) The aqueous liquid preparation according to any one of the above (1) to (3), wherein the concentration of the alkyl aryl polyether alcohol type polymer is selected from a range of minimum concentration of 0.01 w/v % to maximum concentration of 0.5 w/v %,

(7) The aqueous liquid preparation according to any one of the above (1), (2) or (4), wherein the concentration of the polyethylene glycol fatty acid ester is selected from a range of minimum concentration of 0.02 w/v % to maximum concentration of 0.1 w/v %,

(8) The aqueous liquid preparation according to any one of the above (1) to (7), wherein the concentration of the 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof is 0.01 to 0.5 w/v %,

(9) The aqueous liquid preparation according to any one of the above (1) to (8), wherein benzalkonium chloride is contained as a preservative,

(10) The aqueous liquid preparation according to anyone of the above (1) to (9), wherein the pharmacologically acceptable salt of 2-amino-3-(4-bromobenzoyl)phenylacetic acid is a sodium salt,

(11) The aqueous liquid preparation according to any one of the above (1) to (10), wherein the pH of the aqueous liquid preparation is within a range of 7 to 9,

(12) The aqueous liquid preparation according to the above (11), wherein the pH of the aqueous liquid preparation is within a range of 7.5 to 8.5,

(13) The aqueous liquid preparation according to any one of the above (1) to (12), wherein the aqueous liquid preparation is an eye drop,

(14) The aqueous liquid preparation according to any one of the above (1) to (12), wherein the aqueous liquid preparation is a nasal drop,

(15) An eye drop comprising sodium 2-amino-3-(4-bromobenzoyl)phenylacetate hydrate and 0.01 to 0.5 w/v % of tyloxapol,

(16) An eye drop comprising sodium 2-amino-3-(4-bromobenzoyl)phenylacetate hydrate and 0.02 to 0.1 w/v % of polyethylene glycol monostearate,

(17) A method for stabilizing 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof in an aqueous liquid preparation, which comprises incorporating tyloxapol or polyethylene glycol monostearate into an aqueous liquid preparation containing

2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof, and

(18) A method for inhibiting decrease in preservative effect of a preservative in an aqueous liquid preparation of 2-amino-3-(4- bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof, which comprises incorporating tyloxapol or polyethylene glycol monostearate into an aqueous liquid preparation containing 2-amino-3-(4- bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof and a preservative.

According to the present invention, a stable aqueous liquid preparation containing 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof can be prepared by incorporating an alkyl aryl polyether alcohol type polymer such as tyloxapol, or a polyethylene glycol fatty acid ester such as polyethylene glycol monostearate into an aqueous liquid preparation containing 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof. Also, an aqueous liquid preparation of the present invention, wherein a preservative is incorporated, has a sufficient preservative effect.

Therefore, the aqueous liquid preparation of the present invention is advantageously used as an eye drop for the treatment of, for example, blepharitis, conjunctivitis,

scleritis, and postoperative inflammation. In addition, such aqueous liquid preparation can be used as a nasal drop for the treatment of, for example, allergic rhinitis and inflammatory rhinitis (e.g. chronic rhinitis, hypertrophic rhinitis, nasal polyp, etc.).

The pharmacologically acceptable salt of 2-amino-3-(4-bromobenzoyl)phenylacetic acid includes, for example, an alkali metal salt such as sodium salt and potassium salt, and an alkaline earth metal salt such as calcium salt and magnesium salt, among which sodium salt is especially preferable.

2-Amino-3-(4-bromobenzoyl)phenylacetic acid and its pharmacologically acceptable salt can be prepared according to the method as described in JP-A-23052/1977 (corresponding to US patent No. 4,045,576) or by a similar method thereof. These compounds can be obtained as their hydrate depending on synthetic conditions and recrystallization conditions. The hydrate includes 1/2 hydrate, 1 hydrate, and 3/2 hydrate, among which 3/2 hydrate is preferable.

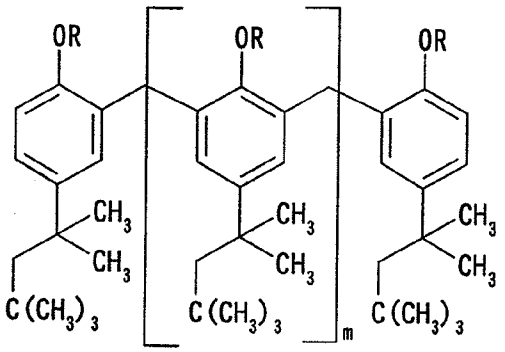
In the aqueous liquid preparation of the present invention, the content (concentration range) of 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof is usually about 0.01 to 0.5 w/v %, preferably about 0.05 to 0.2 w/v %, especially about 0.1 w/v %, and it is preferable to appropriately vary the content depending on the purpose of use and the degree of disease to be treated.

The carbon number of the alkyl in the an alkyl aryl polyether alcohol type polymer which is a non-ionic surfactant

used as a stabilizer for 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof is approximately 1 to 18. Specifically, the alkyl group includes, for example, methyl, ethyl, propyl, isopropyl, cyclopropyl, butyl, isobutyl, sec-butyl, tert-butyl, cyclobutyl, pentyl, isopentyl, neopentyl, tert-pentyl, 1-ethylpropyl, 4-methylpentyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 1,2-dimethylbutyl, 2-ethylbutyl, cyclopentyl, hexyl, cyclohexyl, heptyl, isoheptyl, octyl, isooctyl, nonyl, isononyl, decyl, isodecyl, undecyl, isoundecyl, dodecyl, isododecyl, tridecyl, isotridecyl, tetradecyl, isotetradecyl, pentadecyl, isopentadecyl, hexadecyl, isohexadecyl, heptadecyl, isoheptadecyl, octadecyl, isooctadecyl, and isomers thereof, among which octyl and its isomer (e.g. isooctyl, sec-octyl, 1-methylheptyl, 1-ethylhexyl, 2-ethylhexyl, 1-propylpentyl, 1,5-dimethylhexyl, 1,1,3,3-tetramethylbutyl, etc.) are preferable, and 1,1,3,3-tetramethylbutyl which is an isomer of octyl groups is especially preferable.

The aryl in the alkyl aryl polyether alcohol type polymer can be preferably a phenyl residue. The polyether alcohol can be represented by the formula $O(CH_2CH_2O)_xH$ in which X is an integer of 5 to 100, preferably 5 to 30, more preferably 8 to 10. The average polymerization degree is preferably about 3 to 10.

Among the above-mentioned alkyl aryl polyether alcohol type polymers, tyloxapol having the following formula is especially preferable.



$R=(CH_2CH_2O)xH$
$x=8-10$
$m < 6$

The fatty acid of the polyethylene glycol fatty acid ester which is a non-ionic surfactant used as a stabilizer for 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof can be preferably a fatty acid having the carbon number of 12 to 18. Specific examples of such polyethylene glycol fatty acid esters are polyethylene glycol monostearate (e.g. polyoxyl 8 stearate, polyoxyl 40 stearate, etc.), polyethylene glycol monolaurate, polyethylene glycol monooleate, polyethylene glycol diisostearate, polyethylene glycol dilaurate, polyethylene glycol dioleate, and the like. Among these compounds, polyethylene glycol monostearate is preferable, and polyoxyl 40 stearate is especially preferable. The polyoxyl 40 stearate is a monostearic acid ester of an ethylene oxide condensed polymer, and can be represented by the formula $C_{17}H_{35}COO(CH_2CH_2O)_nH$ which is a non-ionic surfactant and n is about 40.

Although the content (concentration range) of the alkyl aryl polyether alcohol type polymer in the aqueous liquid preparation of the present invention depends on the kind of compounds used, the minimum concentration is about 0.01 w/v %

and the maximum concentration is about 0.5 w/v %. With respect to the tyloxapol content (concentration range), for example, the minimum content is about 0.01 w/v %, 0.02 w/v % or 0.03 w/v %, and the mamximum content is about 0.05 w/v %, 0.1 w/v %, 0.3 w/v % or 0.5 % w/v, and preferably the minimum content is about 0.02 w/v % and the maximum content is about 0.05 w/v %.

Although the content (concentration range) of the polyethylene glycol fatty acid ester in the aqueous liquid preparation of the present invention depends on the kind of compounds used, it is within a range of about 0.02 w/v % of minimum concentration to about 0.1 w/v % of maximum concentration. For example, the content (concentration range) of polyethylene glycol monostearate is within a range of about 0.02 w/v % of minimum content to about 0.1 w/v of maximum content, and preferably within a range of about 0.02 w/v % of the minimum content to about 0.05 w/v % of the maximum content.

The incorporation ratio of tyloxapol in the aqueous liquid preparation of the invention is within a range of the minimum content of about 0.1 or 0.2 part by weight to the maximum content of about 0.5, 1, 3 or 5 parts by weight, relative to 1 part by weight of 2-amino-3-(4-bromobenzoyl)phenylacetic acid or its pharmacologically acceptable salt or a hydrate thereof.

The incorporation ratio of polyethylene glycol monostearate in the aqueous liquid preparation of the present invention is within a range of the minimum content of about 0.2 part by weight to the maximum content of about 0.5 or 1 part by weight, relative to 1 part by weight of

2-amino-3-(4-bromobenzoyl)phenylacetic acid or its pharmacologically acceptable salt or a hydrate thereof.

The preservative used in the present invention includes, for example, quaternary ammonium salts (e.g. benzalkonium chloride, benzethonium chloride, etc.), chlorhexidine gluconate, and the like, among which benzalkonium chloride is especially preferable.

Further, so long as the purpose of the present invention is achieved, conventional various additives such as isotonics, buffers, thickners, stabilizers, chelating agents, pH controlling agents, perfumes and the like may be appropriately added to the aqueous liquid preparation of the present invention. The isotonics include sodium chloride, potassium chloride, glycerine, mannitol, sorbitol, boric acid, glucose, propylene glycol and the like. The buffers include, for example, phosphate buffer, borate buffer, citrate buffer, tartarate buffer, acetate buffer, boric acid, borax, amino acids, and the like. The thickners include polyvinylpyrrolidone, carboxymethylcellulose, carboxypropylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, polyvinyl alcohol, sodium polyacrylate, and the like. The stabilizers include sulfites such as sodium sulfite and the like. The chelating agents include sodium edetate, sodium citrate, condensed sodium phosphate and the like. The pH controlling agents include hydrochloric acid, sodium hydroxide, phosphoric acid, acetic acid and the like. The perfumes include 1-menthol, borneol, camphor, Eucalyptus oil, and the like.

With respect to the concentrations of the above various additives in the aqueous liquid preparation of the present invention,

the isotonic is incorporated into an osmotic pressure ratio of about 0.8 to 1.2, and the concentrations of the buffer and the thickner to be added are about 0.01 to 2 w/v % and 0.1 to 10 w/v %, respectively.

The pH of the aqueous liquid preparation of the present invention is adjusted to about 6 to 9, preferably about 7 to 9, especially about 7.5 to 8.5.

So long as the purpose of the present invention is achieved, other same or different kind of active ingredients may be appropriately added.

The aqueous liquid preparation of the present invention can be prepared by per se known method or according to the method as described in the Japanese Pharmacopoeia、14th Edition, General Rules for Preparations, Solutions or Ophthalmic solutions.

The aqueous liquid preparation of the present invention can be applied to warm-blooded animals such as human, rat, mouse, rabbit, cow, pig, dog, cat, and the like.

The aqueous liquid preparation of the present invention can be prepared easily by dissolving the above-mentioned components in, for example, distilled water or sterile purified water. For example, the aqueous liquid preparation in the form of an eye drop can be used for the treatment of inflammatory diseases in anterior or posterior segment of the eye such as blepharitis, conjunctivitis, scleritis, postoperative

inflammation, and the like. The dose of the aqueous liquid preparation containing 0.1 w/v % of sodium 2-amino-3-(4-bromobenzoyl)phenylacetate hydrate is, for example, administered to an adult 3 to 6 times daily in an amount of 1 to 2 drops per one time. Depending on the degree of diseases, frequency of dosing is appropriately controlled.

BEST MODE FOR CARRYING OUT THE INVENTION

The present invention is illustrated by way of the following Experimental Examples and Working Examples, but it is not restricted by these Examples.

Experimental Example 1: Stability test of sodium 2-amino-3-(4-bromobenzoyl)phenylacetate

Four 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 stability test at 60°C.

Table 1

Component	Comparison Example 1	A-01	A-02	A-03
Sodium 2-amino-3-(4-bromobenzoyl)phenylacetate	0.1 g	0.1 g	0.1 g	0.1 g
Boric acid	1.5 g	1.5 g	1.5 g	1.5 g
Benzalkonium chloride	0.005 g	0.005 g	0.005 g	0.005 g
Polysorbate 80	0.15 g	-	-	-
Polyoxyl 40 stearate	-	0.15 g	-	-
Tyloxapol	-	-	0.15 g	0.02 g
Sterile purified water	q.s.	q.s.	q.s.	q.s
Total volume	100 mL	100 mL	100 mL	100 mL
pH	7.0	7.0	7.0	7.0
Remaining rate (%) at 60 °C after 4 weeks	51.3	63.7	73.8	89.6

The remaining rate (%) in the above Table 1 indicates values obtained by correcting moisture vaporization from the container. As is apparent from the Table 1, stability test was carried out under the conditions of pH 7.0 at 60°C for 4 weeks, and sodium 2-amino-3-(4-bromobenzoyl)phenylacetate in each eye drop was stable in the order of tyloxapol-containing preparation > polyoxyl 40 stearate-containing preparation > polysorbate 80-containing preparation.

Further, with respect to eye drops containing tyloxapol (compositions A-02 and A-03), sodium 2-amino-3-(4-bromobenzoyl)phenylacetate in composition A-03 containing 0.02 w/v % of tyloxapol is more stable than that in composition

A-02 containing 0.15 w/v % of tyloxapol.

Experimental Example 2: Stability test of sodium 2-amino-3-(4-bromobenzoyl)phenylacetate

Five eye drops of sodium 2-amino-3-(4-bromobenzoyl)phenylacetate comprising the components as shown in Table 2 were prepared, filled respectively into a polypropylene container and preserved at 60°C for 4 weeks, and then the content of 2-amino-3-(4-bromobenzoyl)phenylacetic acid and the pH in each eye drop were measured.

Table 2

Components		A−04	A−05	A−06	A−07	A−08
Sodium 2-amino-3-(4-bromobenzoyl)phenyl-acetate		0.1 g	0.1 g	0.1 g	0.1 g	0.1 g
Boric acid		1.1 g	1.1 g	1.1 g	1.1 g	1.1 g
Borax		1.1 g	1.1 g	1.1 g	1.1 g	1.1 g
Benzalkonium chloride		0.005g	0.005g	0.005g	0.005g	0.005g
Polysorbate 80		—	—	—	—	—
Tyloxapol		0.02 g	0.05 g	0.03 g	—	—
Polyoxyl 40 stearate		—	—	—	0.02 g	0.05 g
Polyvinyl-pyrrolidone (K-30)		2.0 g	2.0 g	2.0 g	2.0 g	1.0 g
Sodium edetate		0.02 g	0.02 g	0.02 g	0.02 g	0.02 g
Sodium hydroxide		q.s.	q.s.	q.s.	q.s.	q.s.
Sterile purified water		q.s.	q.s.	q.s.	q.s.	q.s.
Total volume		100 mL	100 mL	100 mL	100 mL	100 mL
pH		8.17	8.16	8.15	8.19	8.19
60°C, 4 weeks	Remaining rate (%)	92.6	90.9	92.0	93.4	93.1
	pH	8.15	8.16	8.15	8.13	8.14

Table 2 shows the remaining rate and the pH of sodium 2-amino-3-(4- bromobenzoyl)phenylacetate after storage at 60°C for 4 weeks, when the remaining rate of sodium 2-amino-3-(4-bromobenzoyl)phenylacetate at the time of production of eye drops is set to 100%. The remaining rate is a value obtained by correcting moisture vaporization from the container. As is

apparent from Table 2, the remaining rate of sodium 2-amino-3-(4-bromobenzoyl)phenylacetate in the compositions A-04, A-05, A-06, A-07 and A-08 containing 0.02 w/v %, 0.03 w/v % and 0.05 w/v % of tyloxapol or 0.02 w/v % and 0.05 w/v % of polyoxyl 40 stearate is not less than 90 % after storage at 60°C for 4 weeks, which indicates that those compositions have sufficient stability for eye drops.

Experimental Example 3: Preservative effect test of aqueous liquid preparation containing sodium 2-amino-3-(4-bromobenzoyl)phenylacetate

Preservative effect test of compositions A-04, A-05 and A-07 of Experimental Example 2 was carried out against *Staphylococcus aureus* (hereinafter referred to as *S. aureus*), *Escherichia Coli* (hereinafter referred to as *E. coli*), *Pseudomonas aeruginosa* (hereinafter referred to as *P. aeruginosa*), *Candida albicans* (hereinafter referred to as *C. albicans*) and *Aspergillus niger* (hereinafter referred to as *A. niger*).

The results are shown in Tables 3-1, 3-2 and 3-3.

Table 3-1

A−04	Cell count (CFU/mL)						
	Inoculum count	6 hours after inoculation	24 hours after inoculation	7 days after inoculation	14 days after inoculation	21 days after inoculation	28 days after inoculation
S. aureus	2.1×10^{6}	3.0×10^{1}	0	0	0	0	0
E. coli	6.5×10^{6}	0	0	0	0	0	0
P. aeruginosa	5.8×10^{6}	0	0	0	0	0	0
C. albicans	3.2×10^{5}	—	—	0	0	0	0
A. niger	1.8×10^{5}	—	—	0	0	0	0

Table 3-2

A−05	Cell count (CFU/mL)						
	Inoculum count	6 hours after inoculation	24 hours after inoculation	7 days after inoculation	14 days after inoculation	21 days after inoculation	28 days after inoculation
S. aureus	2.1×10^{6}	1.7×10^{5}	2.0×10^{1}	0	0	0	0
E. coli	6.5×10^{6}	0	0	0	0	0	0
P. aeruginosa	5.8×10^{6}	0	0	0	0	0	0
C. albicans	3.2×10^{5}	—	—	0	0	0	0
A. niger	1.8×10^{5}	—	—	0	0	0	0

Table 3-3

A−07	Cell count (CFU/mL)						
	Inoculum count	6 hours after inoculation	24 hours after inoculation	7 days after inoculation	14 days after inoculation	21 days after inoculation	28 days after inoculation
S. aureus	2.7×10^6	3.1×10^4	0	0	0	0	0
E. coli	7.4×10^6	0	0	0	0	0	0
P. aeruginosa	8.8×10^6	0	0	0	0	0	0
C. albicans	4.6×10^5	—	—	0	0	0	0
A. niger	1.0×10^5	—	—	0	0	0	0

As is apparent from Tables 3-1, 3-2 and 3-3, the preservative effect of composition A-04 was found to be compatible with EP-criteria A in European Pharmacopoeia (EP), and those of compositions A-05 and A-07 were found to be compatible with EP-criteria B.

The EP-criteria A and EP-criteria B are given in the following.

EP-criteria A:

Viable cell counts of bacteria (*S. aureus, P.aeruginosa*) 6 hours, 24 hours, and 28 days after inoculation decrease to not more than 1/100, not more than 1/1000, and undetectable, respectively.

Viable cell count of fungi (*C. albicans, A. niger*) 7 hours after inoculation decreases to not more than 1/100, and thereafter, the cell count levels off or decreases.

EP-criteria B

Viable cell counts of bacteria (*S. aureus, P.aeruginosa*) 24 hours and 7 days after inoculation decrease to not more than 1/10 and not more than 1/1000, respectively, and thereafter, the cell count levels off or decreases.

Viable cell count of fungi (*C. albicans, A. niger*) 14 days after inoculation decreases to not more than 1/10, and thereafter, the cell count keeps the same level as that of 14 days after inoculation.

Example 1: Eye Drop

Sodium 2-amino-3-(4-bromobenzoyl)phenylacetate 3/2 hydrate	0.1 g
Boric acid	1.1 g
Borax	1.1 g
Benzalkonium chloride	0.005 g
Tyloxapol	0.02 g
Polyvinylpyrrolidone (K-30)	2.0 g
Sodium edetate	0.02 g
Sodium hydroxide	q.s.
Sterile purified water	to make total volume of 100 mL
	pH 8.17

An eye drop is prepared using the above components in a conventional manner.

Example 2: Eye Drop

Sodium 2-amino-3-(4-bromobenzoyl)phenylacetate 3/2 hydrate	0.1 g
Boric acid	1.1 g
Borax	1.1 g
Benzalkonium chloride	0.005 g
Tyloxapol	0.05 g
Polyvinylpyrrolidone (K-30)	2.0 g
Sodium edetate	0.02 g
Sodium hydroxide	q.s.
Sterile purified water	to make total volume of 100 mL
	pH 8.16

An eye drop is prepared using the above components in a conventional manner.

Example 3: Eye Drop

Sodium 2-amino-3-(4-bromobenzoyl)phenylacetate 3/2 hydrate	0.1 g
Boric acid	1.1 g
Borax	1.1 g
Benzalkonium chloride	0.005 g
Polyoxyl 40 stearate	0.02 g
Polyvinylpyrrolidone (K-30)	2.0 g
Sodium edetate	0.02 g
Sodium hydroxide	q.s.
Sterile purified water	to make total volume of 100 mL
	pH 8.19

An eye drop is prepared using the above components in a conventional manner.

INDUSTRIAL APPLICABILITY

The aqueous liquid preparation of the present invention in the form of eye drops is useful for the treatment of blepharitis, conjunctivitis, scleritis, and postoperative inflammation. Such preparation is also useful for the treatment of nasal drop for treatment of, for example, allergic rhinitis and inflammatory rhinitis (e.g. chronic rhinitis, hypertrophic rhinitis, nasal polyp, etc.)

The present application is based on application No. 12427/2003 filed in Japan, and includes the entire contents thereof. By reference, the references including patents and patent applications cited herein are incorporated in the

present application at the same level as when the entire contents thereof are disclosed. Furthermore, since it is obvious that the present invention can be carried out beyond the description of the above explanation and Working Examples, in light of the foregoing description, various other modifications and changes can be made to the present invention, and thus these modifications and changes should be considered to be within the scope of the claims appended hereto.

CLAIMS

1. An aqueous liquid preparation comprising 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof, and an alkyl aryl polyether alcohol type polymer or a polyethylene glycol fatty acid ester.

2. The aqueous liquid preparation according to claim 1, wherein the
alkyl aryl polyether alcohol type polymer has a polymerization degree of 3 to 10, the alkyl contains 1 to 18 carbon atoms, the aryl is a phenyl residue, and the polyether alcohol is represented by the formula $O(CH_2CH_2O)_xH$ in which X is an integer of 5 to 100.

3. The aqueous liquid preparation according to claim 1 or 2, wherein the alkyl aryl polyether alcohol type polymer is tyloxapol.

4. The aqueous liquid preparation according to claim 1, wherein the carbon number of the fatty acid in the polyethylene glycol fatty acid ester is 12 to 18.

5. The aqueous liquid preparation according to claim 1 or 4, wherein the polyethylene glycol fatty acid ester is polyethylene glycol monostearate.

6. The aqueous liquid preparation according to any one of claims 1 to 3, wherein the concentration of the alkyl aryl polyether alcohol type polymer is selected from a range of minimum concentration of 0.01 w/v % to maximum concentration of 0.5 w/v %.

7. The aqueous liquid preparation according to any one of claims 1, 2 or 4, wherein the concentration of the polyethylene glycol fatty acid ester is selected from a range of minimum concentration of 0.02 w/v % to maximum concentration of 0.1 w/v %.

8. The aqueous liquid preparation according to any one of claims 1 to 7, wherein the concentration of the 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof is 0.01 to 0.5 w/v %.

9. The aqueous liquid preparation according to any one of claims 1 to 8, wherein benzalkonium chloride is contained as a preservative.

10. The aqueous liquid preparation according to any one of 1 to 9, wherein the pharmacologically acceptable salt of 2-amino-3-(4-bromobenzoyl)phenylacetic acid is a sodium salt.

11. The aqueous liquid preparation according to any one of claims 1 to 10, wherein the pH of the aqueous liquid preparation is within a range of 7 to 9.

12. The aqueous liquid preparation according to claim 11, wherein the pH of the aqueous liquid preparation is within a range of 7.5 to 8.5.

13. The aqueous liquid preparation according to any one of claims 1 to 12, wherein the aqueous liquid preparation is an eye drop.

14. The aqueous liquid preparation according to any one of claims 1 to 12, wherein the aqueous liquid preparation is a nasal drop.

15. An eye drop comprising sodium 2-amino-3-(4-bromobenzoyl)phenylacetate hydrate and 0.01 to 0.5 w/v % of tyloxapol.

16. An eye drop comprising sodium 2-amino-3-(4-bromobenzoyl)phenylacetate hydrate and 0.02 to 0.1 w/v % of polyethylene glycol monostearate.

17. A method for stabilizing 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof in an aqueous liquid preparation, which comprises incorporating tyloxapol or polyethylene glycol monostearate into an aqueous liquid preparation containing 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate

thereof.

18. A method for inhibiting decrease in preservative effect of a preservative in an aqueous liquid preparation of 2-amino-3-(4- bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof, which comprises incorporating tyloxapol or polyethylene glycol monostearate into an aqueous liquid preparation containing 2-amino-3-(4- bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof and a preservative.

Abstract

An aqueous liquid preparation of the present invention containing 2-amino-3-(4-bromobenzoyl)phenylacetic acid or its pharmacologically acceptable salt or a hydrate thereof, an alkyl aryl polyether alcohol type polymer such as tyloxapol, or a polyethylene glycol fatty acid ester such as polyethylene glycol monostearate is stable. Since even in the case where a preservative is incorporated into said aqueous liquid preparation, the preservative exhibits a sufficient preservative effect for a long time, said aqueous liquid preparation in the form of an eye drop is useful for the treatment of blepharitis, conjunctivitis, scleritis, and postoperative inflammation. Also, the aqueous liquid preparation of the present invention in the form of a nasal drop is useful for the treatment of allergic rhinitis and inflammatory rhinitis (e.g. chronic rhinitis, hypertrophic rhinitis, nasal polyp, etc.).

DECLARATION AND POWER OF ATTORNEY FOR U.S. PATENT APPLICATION

(X) Original ( ) Supplemental ( ) Substitute (X) PCT ( ) Design

As a below named inventor, I hereby declare that: my residence, post office address and citizenship are as stated below next to my name; that I verily believe that I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural inventors are named below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

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

of which is described and claimed in:
( ) the attached specification, or
(X) the specification in the application Serial No. _____, filed February 17, 2005 ;
and with amendments through _____ (if applicable), or
(X) the specification in International Application No. PCT/JP2004/000350, filed January 16, 2004, and as amended on _____ (if applicable).

I hereby state that I have reviewed and understand the content of the above-identified specification, including the claims, as amended by any amendment(s) referred to above.

I acknowledge my duty to disclose to the Patent and Trademark Office all information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, '1.56.

I hereby claim priority benefits under Title 35, United States Code, '119 (and '172 if this application is for a Design) of any application(s) for patent or inventor's certificate listed below and have also identified below any application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

COUNTRY	APPLICATION NO.	DATE OF FILING	PRIORITY CLAIMED
Japan	2003-012427	January 21, 2003	Yes

I hereby claim the benefit under Title 35, United States Code '120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code '112, I acknowledge the duty to disclose information material to patentability as defined in Title 37, Code of Federal Regulations, '1.56 which occurred between the filing date of the prior application and the national or PCT international filing date of this application.

APPLICATION SERIAL NO.	U.S. FILING DATE	STATUS: PATENTED, PENDING, ABANDONED

And I hereby appoint Michael R. Davis, Reg. No. 25,134; Matthew M. Jacob, Reg. No. 25,154; Warren M. Cheek, Jr., Reg. No. 33,367; Nils Pedersen, Reg. No. 33,145; Charles R. Watts, Reg. No. 33,142; and Michael S. Huppert, Reg. No. 40,268, who together constitute the firm of WENDEROTH, LIND & PONACK, L.L.P., as well as any other attorneys and agents associated with Customer No. 000513, to prosecute this application and to transact all business in the U.S. Patent and Trademark Office connected therewith.

I hereby authorize the U.S. attorneys and agents named herein to accept and follow instructions from Iwatani Patent Office, as to any action to be taken in the U.S. Patent and Trademark Office regarding this application without direct communication between the U.S. attorneys and myself. In the event of a change in the persons from whom instructions may be taken, the U.S. attorneys named herein will be so notified by me

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Full Name of Second Inventor	FAMILY NAME FUJITA	FIRST GIVEN NAME Shuhei	SECOND GIVEN NAME	
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Post Office Address	ADDRESS	CITY	STATE OR COUNTRY	ZIP CODE

Full Name of Third Inventor	FAMILY NAME	FIRST GIVEN NAME	SECOND GIVEN NAME	
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Post Office Address	ADDRESS	CITY	STATE OR COUNTRY	ZIP CODE

Full Name of Third Inventor	FAMILY NAME	FIRST GIVEN NAME	SECOND GIVEN NAME	
Residence & Citizenship	CITY	STATE OR COUNTRY	COUNTRY OF CITIZENSHIP	
Post Office Address	ADDRESS	CITY	STATE OR COUNTRY	ZIP CODE

I further declare that all statements made herein of my own knowledge are true, and that all statements 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 issuing thereon.

1st Inventor Shirou Sawa Date March 14, 2005
Shirou SAWA

2nd Inventor Shuhei Fujita Date March 14, 2005
Shuhei FUJITA

3rd Inventor _____ Date _____

4th Inventor _____ Date _____

5th Inventor _____ Date _____

6th Inventor _____ Date _____

The above application may be more particularly identified as follows:

U.S. Application Serial No. _____ Filing Date February 17, 2005

Applicant Reference Number S30F1252(US) Atty Docket No. 2005_0232A

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

PTO/SB/06 (07-06)
Approved for use through 1/31/2007. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number	Filing Date	☐ To be Mailed
13/353,653	01/19/2012	

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY ☐ RATE ($)	SMALL ENTITY ☐ FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =		OR	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =			X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT	01/19/2012	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE ($)	SMALL ENTITY ADDITIONAL FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 18	Minus	** 20	= 0	X $ =		OR	X $60=	0
	Independent (37 CFR 1.16(h))	* 5	Minus	***5	= 0	X $ =		OR	X $250=	0
	☐ Application Size Fee (37 CFR 1.16(s))									
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	0

AMENDMENT		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =		OR	X $ =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =		OR	X $ =	
	☐ Application Size Fee (37 CFR 1.16(s))									
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".

The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

Legal Instrument Examiner:
/ANDREW j. JAMES JR/

PTO/SB/06 (07-06)
Approved for use through 1/31/2007. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number	Filing Date	☐ To be Mailed
13/353,653	01/19/2012	

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY ☐ RATE ($)	SMALL ENTITY FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =		OR	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =			X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT	01/19/2012	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE ($)	SMALL ENTITY ADDITIONAL FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 18	Minus	** 20	= 0	X $ =		OR	X $60=	0
	Independent (37 CFR 1.16(h))	* 5	Minus	***5	= 0	X $ =		OR	X $250=	0
	☐ Application Size Fee (37 CFR 1.16(s))									
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	0

AMENDMENT		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =		OR	X $ =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =		OR	X $ =	
	☐ Application Size Fee (37 CFR 1.16(s))									
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".

The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

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