AO 120 (Rev. 08/10)

TO:	REPORT ON THE FILING OR DETERMINATION OF AN ACTION REGARDING A PATENT OR TRADEMARK
Mail Stop 8 Director of the U.S. Patent and Trademark Office P.O. Box 1450 Alexandria, VA 22313-1450	

In Compliance with 35 U.S.C. § 290 and/or 15 U.S.C. § 1116 you are hereby advised that a court action has been filed in the U.S. District Court for the District of Delaware on the following

☐ Trademarks or ☑ Patents. (☐ the patent action involves 35 U.S.C. § 292.):

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
	1/26/2015	for the District of Delaware

PLAINTIFF	DEFENDANT
SENJU PHARMACEUTICAL CO., LTD., et al.	PADDOCK LABORATORIES, LLC, et al.

	PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1	8,129,431 B2	3/6/2012	Senju Pharmaceutical Co., Ltd.
2	8,669,290 B2	3/11/2014	Senju Pharmaceutical Co., Ltd.
3	8,754,131 B2	6/17/2014	Senju Pharmaceutical Co., Ltd.
4	8,871,813 B2	10/28/2014	Senju Pharmaceutical Co., Ltd.
5	8,917,606 B1	1/6/2015	Senju Pharmaceutical Co., Ltd.

In the above—entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED	INCLUDED BY ☐ Amendment ☐ Answer ☐ Cross Bill ☐ Other Pleading	
PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
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In the above—entitled case, the following decision has been rendered or judgement issued:

DECISION/JUDGEMENT

CLERK	(BY) DEPUTY CLERK	DATE

Copy 1—Upon initiation of action, mail this copy to Director Copy 3—Upon termination of action, mail this copy to Director
Copy 2—Upon filing document adding patent(s), mail this copy to Director Copy 4—Case file copy

AO 120 (Rev. 08/10)

TO:	**Mail Stop 8 Director of the U.S. Patent and Trademark Office P.O. Box 1450 Alexandria, VA 22313–1450**	**REPORT ON THE FILING OR DETERMINATION OF AN ACTION REGARDING A PATENT OR TRADEMARK**

In Compliance with 35 U.S.C. § 290 and/or 15 U.S.C. § 1116 you are hereby advised that a court action has been filed in the **U.S. District Court for the District of New Jersey** on the following:
____ Trademarks or **X** Patents. (____ the patent action involves 35 U.S.C. § 292.)

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
1:14–cv–06893–JBS–KMW	11/3/2014	CAMDEN, NJ

PLAINTIFF	DEFENDANT
SENJU PHARMACEUTICAL CO., LTD.	INNOPHARMA LICENSING, INC.

PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1 8,129,431	3/6/2012	SENJU
2 8,669,290	3/11/2014	SENJU
3 8,754,131	6/17/2014	SENJU
4 8,871,813	10/28/2014	SENJU
5		

In the above––entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED	INCLUDED BY ___ Amendment ___ Answer ___ Cross Bill ___ Other Pleading

PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
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In the above––entitled case, the following decision has been rendered or judgement issued:

DECISION/JUDGEMENT

CLERK	(BY) DEPUTY CLERK	DATE
William T. Walsh	s/ Nicholas Zotti	11/3/2014

Copy 1—Upon initiation of action, mail this copy to Director Copy 3—Upon termination of action, mail this copy to Director
Copy 2—Upon filing document adding patent(s), mail this copy to Director Copy 4—Case file copy

AO 120 (Rev. 08/10)

TO:	REPORT ON THE FILING OR DETERMINATION OF AN ACTION REGARDING A PATENT OR TRADEMARK
Mail Stop 8 Director of the U.S. Patent and Trademark Office P.O. Box 1450 Alexandria, VA 22313-1450	

In Compliance with 35 U.S.C. § 290 and/or 15 U.S.C. § 1116 you are hereby advised that a court action has been filed in the U.S. District Court Eastern District of North Carolina on the following

☐ Trademarks or ☑ Patents. (☐ the patent action involves 35 U.S.C. § 292.):

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
4:14-CV-141-BO	8/8/2014	Eastern District of North Carolina

PLAINTIFF	DEFENDANT
Senju Pharmaceutical Co., Ltd., et al	Metrics, Inc., et al

PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1 US8,129,431 B2	3/6/2012	Senju Pharmaceutical Co., Ltd. - Copy of Complaint included
2 US8,669,290 B2	3/11/2014	Senju Pharmaceutical Co., Ltd.
3 US8,754,131 B2	6/17/2014	Senju Pharmaceutical Co., Ltd.
4		
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In the above—entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED	INCLUDED BY ☐ Amendment ☐ Answer ☐ Cross Bill ☐ Other Pleading	
PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
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AO 120 (Rev. 08/10)

TO:	**Mail Stop 8 Director of the U.S. Patent and Trademark Office P.O. Box 1450 Alexandria, VA 22313–1450**	**REPORT ON THE FILING OR DETERMINATION OF AN ACTION REGARDING A PATENT OR TRADEMARK**

In Compliance with 35 U.S.C. § 290 and/or 15 U.S.C. § 1116 you are hereby advised that a court action has been filed in the **U.S. District Court for the District of New Jersey** on the following:
____ Trademarks or **X** Patents. (____ the patent action involves 35 U.S.C. § 292.)

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
1:14–cv–04964–JBS	8/7/2014	CAMDEN, NJ
PLAINTIFF SENJU PHARMACEUTICAL CO., LTD.		DEFENDANT METRICS, INC.

PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1 8,129,431	3/6/2012	SENJU PHARMACEUTICAL CO., LTD
2 8,669,290	3/11/2014	SENJU PHARMACEUTICAL CO., LTD
3 8,754,131	6/17/2014	SENJU PHARMACEUTICAL CO., LTD
4		
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DATE INCLUDED	INCLUDED BY ___ Amendment ___ Answer ___ Cross Bill ___ Other Pleading

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In the above––entitled case, the following decision has been rendered or judgement issued:

DECISION/JUDGEMENT

CLERK	(BY) DEPUTY CLERK	DATE
William T. Walsh	s/ Brian D. Kemner	8/7/2014

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____ Trademarks or **X** Patents. (____ the patent action involves 35 U.S.C. § 292.)

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
1:14–cv–04149–JBS–KMW	6/26/2014	CAMDEN, NJ
PLAINTIFF SENJU PHARMACEUTICAL CO., LTD.		DEFENDANT LUPIN, LTD.

PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1 8 669 290	3/11/2014	SENJU
2		
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In the above—entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED	INCLUDED BY ___ Amendment ___ Answer ___ Cross Bill ___ Other Pleading	
PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
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William T. Walsh	s/ Nicholas Zotti	6/26/2014

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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 NO.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/687,242	03/11/2014	8669290	2012_5420	1577

513 7590 02/19/2014

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

ISSUE NOTIFICATION

The projected patent number and issue date are specified above.

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

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

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

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

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

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

Shirou SAWA, Hyogo, JAPAN;
Shuhei FUJITA, Hyogo, JAPAN;
SENJU PHARMACEUTICAL CO., LTD., Osaka, JAPAN

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 NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/687,242	11/28/2012	Shirou SAWA	2012_5420	1577

513 7590 02/11/2014

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

EXAMINER	
SOROUSH, LAYLA	
ART UNIT	PAPER NUMBER
1627	

NOTIFICATION DATE	DELIVERY MODE
02/11/2014	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

Notice of Allowability	Application No.	Applicant(s)	
	13/687,242	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 10/22/13*.

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 *19-48*.

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

   * Certified copies not received: _____.

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

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

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

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

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

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
3. ☒ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date 1/15/14,1/17114
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 _____ .
7. ☒ Examiner's Amendment/Comment
8. ☒ Examiner's Statement of Reasons for Allowance
9. ☐ Other _____.

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

Acknowledgement of Receipt

Applicant's response filed on 10/22/2013 to the Office Action mailed on 08/01/2013 is acknowledged.

Claim Status

Claims 19-48 are pending.

Claims 19-48 are allowed.

Withdrawn Rejections

The rejection of claims 44-48 under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph is withdrawn in view of the amendments made to the claims.

The rejection of claims 19, 21-24, 26, 28-30, 32, 34-36, 38, 40-42, and 44-48 under 35 U.S.C. 103(a) as being unpatentable over Gamache, et al. (WO 01/15677 A2; 03/2001) is withdrawn in view of the amendments made to the claims.

The rejection of claims 20, 27, 33, and 39 under 35 U.S.C. 103(a) as being unpatentable over Gamache, et al. (WO 01/15677 A2; 03/2001), as applied to claims 19, 21-24, 26, 28-30, 32, 34-36, 38, 40-42, and 44-48 and further in view of Desai, et al. (5558876) is withdrawn in view of the amendments made to the claims.

The rejection of claims 25, 31, 37, and 43 under 35 U.S.C. 103(a) as being unpatentable over Gamache, et al. (WO 01/15677 A2; 03/2001), as applied to claims 19, 21-24, 26, 28-30, 32, 34-36, 38, 40-42, and 44-48 and further in view of Ogawa, et

al. (US 4910225 A) and De Bruiju et al. (US 6162393 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. 8129431, copending Application No. 13353653 is withdrawn in view of the TD's filed on 11/2/13.

The Double Patenting rejections over copending Application No. 11755662 is withdrawn in view of the abandonment of the case.

EXAMINER'S AMENDMENT

An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

Authorization for this examiner's amendment was given in a telephone interview with Warren M. Cheek on 1/8/14.

The application has been amended as follows:

In claim 26 line 5 after hydrate; insert "the first component is the sole pharmaceutical active ingredient contained in the preparation;"

In claim 27 lines 2-3 after salt delete – , and wherein the first component is the sole pharmaceutical active ingredient contained in the preparation -- .

Reasons for Allowance

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

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

The closest prior arts of record, namely Chen et al. (US 6383471), teach a pharmaceutical composition including a hydrophobic therapeutic agent having at least one ionizable functional group, and a carrier. The carrier includes an ionizing agent capable of ionizing the functional group, a surfactant, and optionally solubilizers, triglycerides, and neutralizing agents (abstract). The reference teaches a hydrophobic therapeutic agent to include bromfenac (2-amino-3-(4-bromobenzoyl)phenalyacetic acid)(see claim 4). The hydrophobic therapeutic agent is used in less than about 1% by weight, and typically less than about 0.1% or 0.01% by weight (see col 4 lines 58-60) (renders obvious the limitation of claims 8 and 24). The reference further teaches surfactants inclusive of polyethylene glycol fatty acid esters and additionally teaches

polyethylene glycol fatty acid monoesters such as peg-15 stearate, etc (see claims 21-22 24 and 27). The surfactants are selected from the group consisting of alcohols; polyoxyethylene alkylethers; fatty acids; glycerol fatty acid esters; acetylated glycerol fatty acid esters; lower alcohol fatty acids esters; polyethylene glycol fatty acids esters; polyethylene glycol glycerol fatty acid esters; polypropylene glycol fatty acid esters; polyoxyethylene glycerides; lactic acid derivatives of mono/diglycerides; propylene glycol diglycerides; sorbitan fatty acid esters; polyoxyethylene sorbitan fatty acid esters; polyoxyethylene-polyoxypropylene block copolymers; transesterified vegetable oils; sterols; sterol derivatives; sugar esters; sugar ethers; sucroglycerides; polyoxyethylene vegetable oils; and polyoxyethylene hydrogenated vegetable oils. The pharmaceutical compositions of the present invention can be provided in the form of a solution preconcentrate; i.e., a composition as described above, and intended to be dispersed with water, either prior to administration, in the form of a drink, or dispersed in vivo (col 34 lines 63-68) (reads on an aqueous liquid preparation). The reference also teaches preservatives (see claim 64). Although formulations specifically suited to oral administration are presently preferred, the compositions of the present invention can also be formulated for topical, transdermal, ocular, pulmonary, vaginal, rectal, transmucosal or parenteral administration (col 35 lines 9-20). Chen et al. further teaches components that can be incorporated into the composition include inorganic acids inclusive of boric acid (col 46, line 6), solubilizer such as polyvinylpyrrolidone (claim 49), exemplifications of carriers comprising Edetate Disodium (col 4 table 20 formulations 65 and 66), and ionizing agents that deprotonate the acidic functional

groups of the therapeutic agent are pharmaceutically acceptable organic or inorganic bases, inclusive of sodium hydroxide (col 11 lines 12-13) (reads on the limitations of claim 22).

However, Applicant presents excellent effects are clearly demonstrated by Experiments 1 to 3 of the present specification. Experiment 1 -- Stability of sodium 2-amino-3-(4-bromobenzoyl)phenyl acetate was evaluated. Namely, two eye drops of sodium 2-amino-3-(4-bromobenzoyl) phenylacetate comprising the components as shown in Table 1 were prepared, filled respectively into a polypropylene container and subjected to a stability test at 60℃ for 4 weeks. As is apparent from Table 1, the stability test was carried out under the conditions of pH 7.0 at 60℃ for 4 weeks. Table 1 clearly shows that sodium 2-amino-3- (4-bromobenzoyl)phenylacetate in polyoxyl 40 stearate-containing preparation was more stable than that in polysorbate 80- containing preparation. As is apparent from Table 2, the remaining rate of sodium 2-amino-3-(4-bromobenzoyl)phenylacetate in the compositions A-07 and A-08 containing 0.02 w/v % and 0.05 w/v % of polyoxyl 40 stearate is not less than 90 % after storage at 60℃ for 4 weeks. Table 2 clearly shows that the compositions containing 0.02 w/v % and 0.05 w/v % of polyoxyl 40 stearate have sufficient stability for eye drops. The arguments are persuasive.

The composition as claimed are found to be patentable over the prior art because the prior art does not teach or fairly suggest a stable aqueous liquid preparation comprising: (a) a first component; and (b) a second component; wherein the first component is 2-amino-3-(4- bromobenzoyl)phenylacetic acid or a

pharmacologically acceptable salt thereof or a hydrate thereof, wherein the hydrate is at least one selected from a 1/2 hydrate, 1 hydrate, and 3/2 hydrate; the first component is the sole pharmaceutical active ingredient contained in the preparation; the second component is tyloxapol and is present in said liquid preparation in an amount sufficient to stabilize said first component; and wherein said stable liquid preparation is formulated for ophthalmic administration.

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	
	13/687,242	SAWA ET AL.	
	Examiner	Art Unit	
	LAYLA SOROUSH	1627	

SEARCHED			
Class	Subclass	Date	Examiner
514	619	1/8/14	LS
514	535	1/8/14	LS
514	570	1/8/14	LS

INTERFERENCE SEARCHED			
Class	Subclass	Date	Examiner
514	**618**	**1/8/14**	**LS**

SEARCH NOTES (INCLUDING SEARCH STRATEGY)		
	DATE	EXMR
STIC (see 13535653); and npl	1/8/14	LS
odp:SAWA, SHIROU and FUJITA, SHUHEI	1/8/14	LS

Sheet 1 of 1

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 15, 2014

ATTY DOCKET NO.	**SERIAL NO.**
2012-5420	13/687,242
FIRST NAMED INVENTOR	
Shirou SAWA	
FILING DATE	**GROUP**
November 28, 2012	1627

U.S. PATENT DOCUMENTS

*EXAMINER INITIAL		DOCUMENT NUMBER	DATE	NAME	CLASS	SUBCLASS	FILING DATE IF APPROPRIATE
/L.S./	AA	4,910,225	3/1990	Ogawa et al.			
/L.S./	AB	6,274,609	8/2001	Yasueda et al.			
	AC						
	AD						
	AE						
	AF						
	AG						
	AH						
	AI						

FOREIGN PATENT DOCUMENTS

		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION YES	TRANSLATION NO
	BA	0 306 984	3/1989	EP				
	BB							
	BC							
	BD							
	BE							

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

/L.S./	CA	H. Scott et al., "Comparing the Surface Chemical Properties and the Effect of Salts on the Cloud Point of a Conventional Nonionic Surfactant, Octoxynol 9 (Triton X-100), and of its Oligomer, Tyloxapol (Triton WR-1339)", Journal of Colloid and Interface Science, Vol. 205, pp. 496-502, 1998.
	CB	
	CC	
	CD	

EXAMINER	/Layla Soroush/	DATE CONSIDERED

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

Sheet 1 of 1

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 17, 2014

ATTY DOCKET NO.	**SERIAL NO.**
2012-5420	13/687,242
FIRST NAMED INVENTOR	
Shirou SAWA	
FILING DATE	**GROUP**
November 28, 2012	1627

U.S. PATENT DOCUMENTS

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/L.S./	AB	6,274,609	8/2001	Yasueda et al.			
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	AD						
	AE						
	AF						
	AG						
	AH						
	AI						

FOREIGN PATENT DOCUMENTS

		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION YES	TRANSLATION NO
	BA	0 306 984	3/1989	EP				
	BB							
	BC							
	BD							
	BE							

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

/L.S./	CA	H. Scott et al., "Comparing the Surface Chemical Properties and the Effect of Salts on the Cloud Point of a Conventional Nonionic Surfactant, Octoxynol 9 (Triton X-100), and of its Oligomer, Tyloxapol (Triton WR-1339)", Journal of Colloid and Interface Science, Vol. 205, pp. 496-502, 1998.
	CB	
	CC	
	CD	

EXAMINER	/Layla Soroush/	DATE CONSIDERED

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

Issue Classification	Application/Control No. 13/687,242	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/ 2/6/14	Total Claims Allowed: 30	
(Legal Instruments Examiner) (Date)	(Primary Examiner) (Date)	O.G. Print Claim(s) 1	O.G. Print Fig. NONE

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

Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original
	1	13	31		61		91		121		151		181
	2	14	32		62		92		122		152		182
	3	15	33		63		93		123		153		183
	4	16	34		64		94		124		154		184
	5	17	35		65		95		125		155		185
	6	18	36		66		96		126		156		186
	7	19	37		67		97		127		157		187
	8	20	38		68		98		128		158		188
	9	21	39		69		99		129		159		189
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	11	23	41		71		101		131		161		191
	12	24	42		72		102		132		162		192
	13	25	43		73		103		133		163		193
	14	26	44		74		104		134		164		194
	15	27	45		75		105		135		165		195
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	17	29	47		77		107		137		167		197
	18	30	48		78		108		138		168		198
1	19		49		79		109		139		169		199
2	20		50		80		110		140		170		200
3	21		51		81		111		141		171		201
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5	23		53		83		113		143		173		203
6	24		54		84		114		144		174		204
7	25		55		85		115		145		175		205
8	26		56		86		116		146		176		206
9	27		57		87		117		147		177		207
10	28		58		88		118		148		178		208
11	29		59		89		119		149		179		209
12	30		60		90		120		150		180		210

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 01/13/2014
WENDEROTH, LIND & PONACK, L.L.P.
1030 15th Street, N.W.,
Suite 400 East
Washington, DC 20005-1503

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

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

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

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/687,242	11/28/2012	Shiroo SAWA	2012_5420	1577

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

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$960	$0	$0	$960	04/15/2014

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.

WENDEROTH, LIND & PONACK, L.L.P.
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: 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 .....

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- ☒ The Director is hereby authorized to charge the required fee(s), any deficiency, or credits any overpayment, to Deposit Account Number 23-0975 (enclose an extra copy of this form).

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

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

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

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

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

/Warren M. Cheek, Jr./ Digitally signed by /Warren M. Cheek, Jr./
DN: cn=/Warren M. Cheek, Jr./, o=, ou=, email=wcheek@wenderoth.com, c=US
Date: 2014.01.22 13:39:24 -05'00'

Authorized Signature ..... Date January 22, 2014

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

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

Electronic Patent Application Fee Transmittal

Application Number:	13687242
Filing Date:	28-Nov-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_5420

Filed as Large Entity

Utility under 35 USC 111(a) Filing Fees

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

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

Electronic Acknowledgement Receipt

EFS ID:	17989977
Application Number:	13687242
International Application Number:	
Confirmation Number:	1577
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_5420
Receipt Date:	22-JAN-2014
Filing Date:	28-NOV-2012
Time Stamp:	16:00:57
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Credit Card
Payment was successfully received in RAM	$960
RAM confirmation Number	2548
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	522364 38f9217f43982b65db57cb8acc9e13a27ad38615	no	1

Warnings:

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

Information:

2	Fee Worksheet (SB06)	fee-info.pdf	30913 f4efd9fade24378f9d8990d477a5c298f54fd089	no	2

Warnings:

Information:

Total Files Size (in bytes):	553277

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

New Applications Under 35 U.S.C. 111

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

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

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

New International Application Filed with the USPTO as a Receiving Office

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

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Named Inventor	:	Attorney Docket No. 2012-5420
Shirou SAWA	:	**Confirmation No. 1577**
Serial No. 13/687,242	:	Group Art Unit 1627
Filed November 28, 2012	:	Examiner Layla Soroush
AQUEOUS LIQUID PREPARATION CONTAINING 2-AMINO-3-(4-BROMOBENZOYL)PHENYLACETIC ACID	:	**Mail Stop: AMENDMENT**

INFORMATION DISCLOSURE STATEMENT

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

Sir/Madam:

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

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

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

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

and thus no certification and/or fee is required.

1b. [] This Information Disclosure Statement is submitted

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

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

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

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

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

the certification of paragraph 2 below is provided, and

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

2. It is hereby certified

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

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

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

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

b. [] an International Search Report submitted herewith,

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

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

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

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

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

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

Respectfully submitted,

/Warren M. Cheek, Jr./

Digitally signed by /Warren M. Cheek, Jr./
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January 17, 2014

Sheet 1 of 1

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 17, 2014

ATTY DOCKET NO.	**SERIAL NO.**
2012-5420	13/687,242
FIRST NAMED INVENTOR	
Shirou SAWA	
FILING DATE	**GROUP**
November 28, 2012	1627

U.S. PATENT DOCUMENTS

*EXAMINER INITIAL		DOCUMENT NUMBER	DATE	NAME	CLASS	SUBCLASS	FILING DATE IF APPROPRIATE
	AA	4,910,225	3/1990	Ogawa et al.			
	AB	6,274,609	8/2001	Yasueda et al.			
	AC						
	AD						
	AE						
	AF						
	AG						
	AH						
	AI						

FOREIGN PATENT DOCUMENTS

		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION YES	TRANSLATION NO
	BA	0 306 984	3/1989	EP				
	BB							
	BC							
	BD							
	BE							

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

	CA	H. Scott et al., "Comparing the Surface Chemical Properties and the Effect of Salts on the Cloud Point of a Conventional Nonionic Surfactant, Octoxynol 9 (Triton X-100), and of its Oligomer, Tyloxapol (Triton WR-1339)", Journal of Colloid and Interface Science, Vol. 205, pp. 496-502, 1998.
	CB	
	CC	
	CD	

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.

(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **0 306 984 A1**

(12) EUROPEAN PATENT APPLICATION

(21) Application number: **88114804.3**

(51) Int. Cl.4: **A61K 9/06 , A61K 47/00**

(22) Date of filing: **09.09.88**

(30) Priority: **11.09.87 US 96173**

(43) Date of publication of application:
15.03.89 Bulletin 89/11

(84) Designated Contracting States:
AT BE CH DE FR GB IT LI LU NL SE

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Siegfriedstrasse 8
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(54) Preservative system forophthalmic formulations.

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

EP 0 306 984 A1

PRESERVATIVE SYSTEM FOR OPHTHALMIC FORMULATIONS

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

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

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

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

Organo-mercurials (e.g., thimerosal, phenylmercuric acetate and phenylmercuric nitrate) have been used extensively as the preservative in ophthalmic solutions. These compounds, however, pose difficulties due to potential mercury toxicity as well as poor chemical stability. Benzalkonium chloride, a quaternary ammonium compound, has been widely used in ophthalmic solutions, and is considered to be the preservative of choice. However, BAC has typically been considered to be incompatible with anionic drugs (e.g., salicylates or nitrates, etc.), forming insoluble complexes which cause the solution to become cloudy or turbid. Such a complex between the anionic drug and benzalkonium chloride can cause a decrease in the pharmaceutical activity of the anionic drug.

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

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

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

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

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

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

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

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

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

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

Definitions

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

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

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

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

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

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

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

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

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

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

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

Formulations

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

methods readily known to those skilled in the art.

Pharmaceutical ophthalmic formulations typically contain an effective amount, e.g., 0.001% to 10% wt/vol., preferably 0.002% to 5% wt/vol, most preferably 0.005% to 1% wt/vol of an active ingredient (e.g., the NSAID of the present invention). The amount of active ingredient will vary with the particular formulation and the disease state for which it is intended. The total concentration of solutes should be such that, if possible, the resulting solution is isotonic with the lacrimal fluid (though this is not absolutely necessary) and has a pH in the range of 6 to 8.

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

Ingredient	Amount
Active Agent	0.001% to 10.0% wt/vol.;
Preservative	0.001% to 1.0% wt/vol.;
Surfactant	0.001% to 1.0% wt/vol.;
Other Excipients	0% to 10.0% wt/vol.; and
Purified Water	q.s. to 100%.

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

Ingredient	Amount
Chelating agent	0.01% to 1.0%wt/vol.;
Tonicifier	q.s. to achieve isotonicity with lacrimal fluid; and
1N NaOH or 1N HCl	q.s. to adjust pH to 6.0 to 8.0.

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

Ingredient	Amount
NSAID	0.002% to 5.0% wt/vol.;
BAC (50% aq. soln.)	0.002% to 1.0% wt/vol.;
Octoxynol 40 (70% aq. soln.)	0.001% to 1.0% wt/vol.;
EDTA Na_2	0.01% to 1.0% wt/vol.;
NaCl	q.s. for isotonicity with lacrimal fluid;
1N NaOH or 1N HCl	q.s. to adjust pH to 7.4±0.4; and
Purified Water	q.s. to 100%.

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

Ingredient	Amount
NSAID	0.005% to 1.0% wt/vol.;
BAC (50% aq. soln.)	0.002% to 1.0% wt/vol.;
Octoxynol 40 (70% aq. soln.)	0.001% to 1.0% wt/vol.;
EDTA Na_2	0.01% to 1.0% wt/vol.;
NaCl	q.s. for isotonicity with lacrimal fluid;
1N NaOH or 1N HCl	q.s. to adjust pH to 7.4±0.4; and
Purified Water	q.s. to 100%.

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

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

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

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

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

The nonionic surfactants useful in the formulations of the present invention are preferably ethoxylated octylphenol compounds, such as octylphenoxypoly-(ethyleneoxy)ethanols, more preferably, a homologous series of surfactants sold under the trade name Igepal CA with a numerical suffix indicating the mole ratio of ethylene oxide to octylphenol, the ratio being 3 to 40. Examples include Octoxynol 9, Octoxynol 12, Octoxynol 13, and Octoxynol 40, and most preferably Octoxynol 40, manufactured and sold by GAF under the trade name Igepal CA897 (a 70% aqueous solution of Octoxynol 40).

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

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

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

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

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

These formulations are prepared by dissolving the solutes (e.g., the NSAID, the preservative, the surfactant, the chelating agent, and the buffering agent) in a suitable quantity of water, adjusting the pH to about 6 to 8, preferably 6.8 to 8.0 and most preferably 7.4, making a final volume adjustment to 100% with additional water, and sterilizing the preparation using any suitable method known to those in the art.

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

Preferred Formulations

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

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

The preferred preservative of the invention is benzalkonium chloride.

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

chloride as the preservative.

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

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

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

Ingredient	Amount
NSAID	0.002% to 5.0% wt/vol.;
BAC (50% aq. soln.)	0.002% to 1.0% wt/vol.;
Octoxynol 40 (70% aq. soln.)	0.001% to 1.0% wt/vol.;
EDTA Na_2	0.01% to 1.0% wt/vol.;
NaCl	q.s. for isotonicity with lacrimal fluid;
1N NaOH or 1N HCl	q.s. to adjust pH to 7.4±0.4; and
Purified Water	q.s. to 100%.

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

Ingredient	Amount
NSAID	0.005% to 1.0% wt/vol.;
BAC (50% aq. soln.)	0.002% to 1.0% wt/vol.;
Octoxynol 40 (70% aq. soln.)	0.001% to 1.0% wt/vol.;
EDTA Na_2	0.01% to 1.0% wt/vol.;
NaCl	q.s. for isotonicity with lacrimal fluid;
1N NaOH or 1N HCl	q.s. to adjust pH to 7.4±0.4; and
Purified Water	q.s. to 100%.

A preferred ophthalmic NSAID solution has the following formulation:

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

Most preferred is the ophthalmic solution according to the above formulation wherein the NSAID is Ketorolac Tromethamine or an isomer thereof.

Utility and Administration

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

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

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

suspensions or ointments, or by subconjunctival injection.

The dosage level will, of course, depend on the concentration of the drops, the condition of the subject and the individual magnitude of responses to treatment. However, typical dosage ranges might be about 2 to 10 drops of 0.5% solution of active ingredient per day.

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

Testing

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

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

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

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

EXAMPLE 1

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

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

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

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

EXAMPLE 2

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

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

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

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

EXAMPLE 3

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

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

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

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

EXAMPLE 4

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

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

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

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

EXAMPLE 5

Physical stability of the formulations of the present invention is measured by preparing clear formulations, in the concentrations shown in the table below, sealing them in sterilized containers, and observing the clarity of the solution after a period of one month and again after five months. Solutions that remain clear are considered stable in this procedure.

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

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

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

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

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

EXAMPLE 6

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

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

EXAMPLE 7

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

Ophthalmic examinations were performed preoperatively (within 3 weeks of surgery) and during the first

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

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

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

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

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

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

129 patients began treatment for 21 days with either ketorolac or vehicle. In this study, the ketorolac formulation used was that illustrated in Example 1 above. During the first week 118 patients and during the second week 110 patients were evaluated for postoperative inflammation with ophthalmic examinations and fluorophotometry. During the third week, 83 patients were evaluated with ophthalmic examinations alone. At 2 weeks ketorolac provide significantly greater anti-inflammatory activity than the vehicle as measured by fluorophotometry ($p = 0.019$). When patients were excluded who had greater than 40% difference in fluorescein concentration between eyes at baseline, the p-value during week 2 rose to 0.06. In addition, the vehicle-treated patients had more ocular inflammation seen on slit lamp examination, e.g., eyelid edema ($p = 0.001$), conjunctival injection ($p = 0.001$), and Descemet folds ($p = 0.002$) than did the ketorolac-treated patients. Finally, there were significantly more complaints ($p = 0.01$) and more sever complaints consistent with ocular inflammation (photophobia, iritis, conjunctival injection) in the vehicle-treated group than in the ketorolac-treated group.

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

EXAMPLE 8

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

Thirty patients with allergic conjunctivitis participated in the study. Following admission to the study, patients reported to the investigator for baseline, mid-week, and final one-week examinations. At each of these visits, patients received ophthalmic examinations (visual acuity, external eye exam using slit lamp biomicroscopy, measurement of intraocular pressure, and undilated ophthalmoscopic examination). Laboratory tests included a conjunctival scraping performed at baseline and the final exam.

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

Fisher's Exact Test. two-tailed).

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

EXAMPLE 9

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

EXAMPLE 10

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

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

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

Claims

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

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

3. The ophthalmic NSAID formulation of any one of Claims 1 and 2 wherein said nonionic ethoxylated octylphenol surfactant is an octylphenoxypoly(ethyleneoxy)-ethanol with a mole ratio of ethylene oxide to octylphenol of between 3:1 and 40:1.

4. The ophthalmic NSAID formulation of any one of Claims 1 to 3 wherein said nonionic ethoxylated octylphenol surfactant is Octoxynol 40.

5. The ophthalmic NSAID formulation of any one of Claims 1 to 4 including disodium edetate.

6. The ophthalmic NSAID formulation of any one of Claims 1 to 5 wherein said NSAID is selected from the group: ketorolac, indomethacin, flurbiprofen, and diclofenac, or their isomers, pharmaceutically acceptable salts, or esters.

7. The ophthalmic NSAID formulation of any one of Claims 1 to 6 wherein said NSAID is Ketorolac Tromethamine.

8. The ophthalmic NSAID formulation of any one of Claims 1 to 6 wherein said NSAID is the (1)-isomer of ketorolac or one of its pharmaceutically acceptable salts.

9. The ophthalmic NSAID formulation of any one of Claims 1 to 8 comprising:

NSAID	0.001% to 10.0% wt/vol.;
Preservative	0.001% to 1.0% wt/vol.;

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

10. The ophthalmic NSAID formulation of Claim 9 including:
Chelating agent 0.01% to 1.0%wt/vol.;
Tonicifier q.s. to achieve isotonicity with lacrimal fluid; and
1N NaOH or 1N HCl q.s. to adjust pH to 6.0 to 8.0.

11. The ophthalmic NSAID formulation of Claim 10 comprising:
NSAID 0.50% wt/vol.;
BAC(50% aq. soln.) 0.02% wt/vol.;
Octoxynol 40 (70% aq. soln.) 0.01% wt/vol.;
EDTA Na_2 0.10% wt/vol.;
NaCl 0.79% wt/vol.;
1N NaOH or 1N HCl q.s. to adjust pH to 7.4±0.4; and
Purified Water q.s. to 100%.

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

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

14. The preservative system of Claim 13 wherein said preservative is benzalkonium chloride and said surfactant is Octoxynol 40.

15. The use of a formulation of any one of Claims 1 to 12 for the manufacture of a medicament for the treatment or prevention of ophthalmic diseases, particularly ocular inflammatory diseases.

16. The use of a preservative system of any one of Claims 13 and 14 for manufacture of a medicament for the treatment or prevention of ophthalmic diseases, particularly ocular inflammatory diseases.

17. A process for the preparation of an ophthalmic NSAID formulation which comprises mixing
0.001% to 10.0% wt/vol. of an NSAID,
0.001% to 1.0% wt/vol. of a preservative,
0.001% to 1.0% wt/vol. of a nonionic ethoxylated octylphenol surfactant, and
Purified Water q.s. to 100%.

18. The process of Claim 17 which further comprises mixing
0.01% to 1.0%wt/vol. of a chelating agent,
q.s. of a tonicifier to achieve isotonicity with lacrimal fluid, and
q.s. of 1N NaOH or 1N HCl to adjust pH to 6.0 to 8.0.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number

EP 88 11 4804

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.4)
Y	DE-A-3 026 402 (SYNTEX) * Claims; page 9, line 31; page 10, lines 15-19 *	1-7,9-16	A 61 K 9/06 A 61 K 47/00
Y	US-A-4 087 538 (J.B. PORTNOFF) * Claims; column 2, lines 34-36,47-51; column 3, lines 36-40,53 *	1-7,9-16	
Y	CHEMICAL ABSTRACTS, vol. 88, no. 25, 19th June 1978, page 166, no. 183735c, Columbus, Ohio, US; M.T. NADIR et al.: "Influence of (ethoxy)5 octyl phenon on the antibacterial properties of preservatives", & J. PHARM. PHARMACOL. 1977, 29(SUPPL., BR. PHARM. CONF. 1977), 67P * Abstract *	1-7,9-16	
A	WO-A-8 504 106 (J. CORBIERE) * Claims 1-2,5,7 *	1-7,9-16	

TECHNICAL FIELDS SEARCHED (Int. Cl.4)

A 61 K

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	23-11-1988	SCARPONI U.

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

EPO FORM 1503 03.82 (P0401)

Electronic Patent Application Fee Transmittal

Application Number:	13687242
Filing Date:	28-Nov-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_5420

Filed as Large Entity

Utility under 35 USC 111(a) Filing Fees

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

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
Submission- Information Disclosure Stmt	1806	1	180	180
		Total in USD ($)		**180**

Electronic Acknowledgement Receipt

EFS ID:	17944031
Application Number:	13687242
International Application Number:	
Confirmation Number:	1577
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_5420
Receipt Date:	17-JAN-2014
Filing Date:	28-NOV-2012
Time Stamp:	14:18:02
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Credit Card
Payment was successfully received in RAM	$180
RAM confirmation Number	595
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	Information Disclosure Statement (IDS) Form (SB08)	AttachZ1_IDS.pdf	186266 e078c6768583bfde12b776471ecb5826c24b83e8	no	3

Warnings:

Information:

This is not an USPTO supplied IDS fillable form

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.

2	Information Disclosure Statement (IDS) Form (SB08)	AttachZ2_SB08.pdf	120345 268b9fc8323e83fa8308e8df8108ea049decb618	no	1

Warnings:

Information:

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3	Foreign Reference	AttachZBA.pdf	775776 d14702bcaa080ba72fd9c466b88870f4d459d208	no	13

Warnings:

Information:

4	Non Patent Literature	AttachZCA.pdf	4779724 acd56775ad00351d84f658fec748de5ac3c33eb9	no	7

Warnings:

Information:

5	Fee Worksheet (SB06)	fee-info.pdf	30954 f7e7d99bf32c9427111ce659c0252631bd0275cd	no	2

Warnings:

Information:

Total Files Size (in bytes):	5893065

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
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

NOTICE OF ALLOWANCE AND FEE(S) DUE

513 7590 01/15/2014

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

EXAMINER
SOROUSH, LAYLA

ART UNIT	PAPER NUMBER
1627	

DATE MAILED: 01/15/2014

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/687,242	11/28/2012	Shirou SAWA	2012_5420	1577

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

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$960	$0	$0	$960	04/15/2014

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

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

HOW TO REPLY TO THIS NOTICE:

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

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

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

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

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

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

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

PART B - FEE(S) TRANSMITTAL

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

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

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

513 7590 01/15/2014
WENDEROTH, LIND & PONACK, L.L.P.
1030 15th Street, N.W.,
Suite 400 East
Washington, DC 20005-1503

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

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

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

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/687,242	11/28/2012	Shirou SAWA	2012_5420	1577

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

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$960	$0	$0	$960	04/15/2014

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

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

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

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

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

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

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

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

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

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

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

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

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

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/687,242	11/28/2012	Shirou SAWA	2012_5420	1577

513 7590 01/15/2014

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

EXAMINER	
SOROUSH, LAYLA	
ART UNIT	PAPER NUMBER
1627	

DATE MAILED: 01/15/2014

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.

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

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

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

Privacy Act Statement

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

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

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

Examiner-Initiated Interview Summary	Application No.	Applicant(s)	
	13/687,242	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: *1/8/14*.

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

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

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

☐ Attachment

/Layla Soroush/ Examiner, Art Unit 1627	

Notice of Allowability	Application No.	Applicant(s)	
	13/687,242	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 10/22/13*.

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 *19-48*.

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

   * Certified copies not received: _____.

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

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

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

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

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

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
3. ☐ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date _____
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 *1/8/13* .
7. ☒ Examiner's Amendment/Comment
8. ☒ Examiner's Statement of Reasons for Allowance
9. ☐ Other _____.

/LAYLA SOROUSH/
Primary Examiner, Art Unit 1627

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

Acknowledgement of Receipt

Applicant's response filed on 10/22/2013 to the Office Action mailed on 08/01/2013 is acknowledged.

Claim Status

Claims 19-48 are pending.

Claims 19-48 are allowed.

Withdrawn Rejections

The rejection of claims 44-48 under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph is withdrawn in view of the amendments made to the claims.

The rejection of claims 19, 21-24, 26, 28-30, 32, 34-36, 38, 40-42, and 44-48 under 35 U.S.C. 103(a) as being unpatentable over Gamache, et al. (WO 01/15677 A2; 03/2001) is withdrawn in view of the amendments made to the claims.

The rejection of claims 20, 27, 33, and 39 under 35 U.S.C. 103(a) as being unpatentable over Gamache, et al. (WO 01/15677 A2; 03/2001), as applied to claims 19, 21-24, 26, 28-30, 32, 34-36, 38, 40-42, and 44-48 and further in view of Desai, et al. (5558876) is withdrawn in view of the amendments made to the claims.

The rejection of claims 25, 31, 37, and 43 under 35 U.S.C. 103(a) as being unpatentable over Gamache, et al. (WO 01/15677 A2; 03/2001), as applied to claims 19, 21-24, 26, 28-30, 32, 34-36, 38, 40-42, and 44-48 and further in view of Ogawa, et

al. (US 4910225 A) and De Bruiju et al. (US 6162393 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. 8129431, copending Application No. 13353653 is withdrawn in view of the TD's filed on 11/2/13.

The Double Patenting rejections over copending Application No. 11755662 is withdrawn in view of the abandonment of the case.

EXAMINER'S AMENDMENT

An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

Authorization for this examiner's amendment was given in a telephone interview with Warren M. Cheek on 1/8/14.

The application has been amended as follows:

In claim 26 line 5 after hydrate; insert "the first component is the sole pharmaceutical active ingredient contained in the preparation;"

In claim 27 lines 2-3 after salt delete – , and wherein the first component is the sole pharmaceutical active ingredient contained in the preparation -- .

Reasons for Allowance

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

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

The closest prior arts of record, namely Chen et al. (US 6383471), teach a pharmaceutical composition including a hydrophobic therapeutic agent having at least one ionizable functional group, and a carrier. The carrier includes an ionizing agent capable of ionizing the functional group, a surfactant, and optionally solubilizers, triglycerides, and neutralizing agents (abstract). The reference teaches a hydrophobic therapeutic agent to include bromfenac (2-amino-3-(4-bromobenzoyl)phenalyacetic acid)(see claim 4). The hydrophobic therapeutic agent is used in less than about 1% by weight, and typically less than about 0.1% or 0.01% by weight (see col 4 lines 58-60) (renders obvious the limitation of claims 8 and 24). The reference further teaches surfactants inclusive of polyethylene glycol fatty acid esters and additionally teaches

polyethylene glycol fatty acid monoesters such as peg-15 stearate, etc (see claims 21-22 24 and 27). The surfactants are selected from the group consisting of alcohols; polyoxyethylene alkylethers; fatty acids; glycerol fatty acid esters; acetylated glycerol fatty acid esters; lower alcohol fatty acids esters; polyethylene glycol fatty acids esters; polyethylene glycol glycerol fatty acid esters; polypropylene glycol fatty acid esters; polyoxyethylene glycerides; lactic acid derivatives of mono/diglycerides; propylene glycol diglycerides; sorbitan fatty acid esters; polyoxyethylene sorbitan fatty acid esters; polyoxyethylene-polyoxypropylene block copolymers; transesterified vegetable oils; sterols; sterol derivatives; sugar esters; sugar ethers; sucroglycerides; polyoxyethylene vegetable oils; and polyoxyethylene hydrogenated vegetable oils. The pharmaceutical compositions of the present invention can be provided in the form of a solution preconcentrate; i.e., a composition as described above, and intended to be dispersed with water, either prior to administration, in the form of a drink, or dispersed in vivo (col 34 lines 63-68) (reads on an aqueous liquid preparation). The reference also teaches preservatives (see claim 64). Although formulations specifically suited to oral administration are presently preferred, the compositions of the present invention can also be formulated for topical, transdermal, ocular, pulmonary, vaginal, rectal, transmucosal or parenteral administration (col 35 lines 9-20). Chen et al. further teaches components that can be incorporated into the composition include inorganic acids inclusive of boric acid (col 46, line 6), solubilizer such as polyvinylpyrrolidone (claim 49), exemplifications of carriers comprising Edetate Disodium (col 4 table 20 formulations 65 and 66), and ionizing agents that deprotonate the acidic functional

groups of the therapeutic agent are pharmaceutically acceptable organic or inorganic bases, inclusive of sodium hydroxide (col 11 lines 12-13) (reads on the limitations of claim 22).

However, Applicant presents excellent effects are clearly demonstrated by Experiments 1 to 3 of the present specification. Experiment 1 -- Stability of sodium 2-amino-3-(4-bromobenzoyl)phenyl acetate was evaluated. Namely, two eye drops of sodium 2-amino-3-(4-bromobenzoyl) phenylacetate comprising the components as shown in Table 1 were prepared, filled respectively into a polypropylene container and subjected to a stability test at 60℃ for 4 weeks. As is apparent from Table 1, the stability test was carried out under the conditions of pH 7.0 at 60℃ for 4 weeks. Table 1 clearly shows that sodium 2-amino-3- (4-bromobenzoyl)phenylacetate in polyoxyl 40 stearate-containing preparation was more stable than that in polysorbate 80- containing preparation. As is apparent from Table 2, the remaining rate of sodium 2-amino-3-(4-bromobenzoyl)phenylacetate in the compositions A-07 and A-08 containing 0.02 w/v % and 0.05 w/v % of polyoxyl 40 stearate is not less than 90 % after storage at 60℃ for 4 weeks. Table 2 clearly shows that the compositions containing 0.02 w/v % and 0.05 w/v % of polyoxyl 40 stearate have sufficient stability for eye drops. The arguments are persuasive.

The composition as claimed are found to be patentable over the prior art because the prior art does not teach or fairly suggest a stable aqueous liquid preparation comprising: (a) a first component; and (b) a second component; wherein the first component is 2-amino-3-(4- bromobenzoyl)phenylacetic acid or a

pharmacologically acceptable salt thereof or a hydrate thereof, wherein the hydrate is at least one selected from a 1/2 hydrate, 1 hydrate, and 3/2 hydrate; the first component is the sole pharmaceutical active ingredient contained in the preparation; the second component is tyloxapol and is present in said liquid preparation in an amount sufficient to stabilize said first component; and wherein said stable liquid preparation is formulated for ophthalmic administration.

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

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

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

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should

you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Layla Soroush/

Examiner, Art Unit 1627

Examiner-Initiated Interview Summary	Application No.	Applicant(s)	
	13/687,242	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: *1/8/14*.

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

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

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

☐ Attachment

/Layla Soroush/ Examiner, Art Unit 1627	

Issue Classification	Application/Control No. 13/687,242	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/ 1/8/13 (Primary Examiner) (Date)	Total Claims Allowed: 30	
(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	13	31		61		91		121		151		181
	2	14	32		62		92		122		152		182
	3	15	33		63		93		123		153		183
	4	16	34		64		94		124		154		184
	5	17	35		65		95		125		155		185
	6	18	36		66		96		126		156		186
	7	19	37		67		97		127		157		187
	8	20	38		68		98		128		158		188
	9	21	39		69		99		129		159		189
	10	22	40		70		100		130		160		190
	11	23	41		71		101		131		161		191
	12	24	42		72		102		132		162		192
	13	25	43		73		103		133		163		193
	14	26	44		74		104		134		164		194
	15	27	45		75		105		135		165		195
	16	28	46		76		106		136		166		196
	17	29	47		77		107		137		167		197
	18	30	48		78		108		138		168		198
1	19		49		79		109		139		169		199
2	20		50		80		110		140		170		200
3	21		51		81		111		141		171		201
4	22		52		82		112		142		172		202
5	23		53		83		113		143		173		203
6	24		54		84		114		144		174		204
7	25		55		85		115		145		175		205
8	26		56		86		116		146		176		206
9	27		57		87		117		147		177		207
10	28		58		88		118		148		178		208
11	29		59		89		119		149		179		209
12	30		60		90		120		150		180		210

Search Notes	Application/Control No.	Applicant(s)/Patent under Reexamination	
	13/687,242	SAWA ET AL.	
	Examiner	Art Unit	
	LAYLA SOROUSH	1627	

SEARCHED			
Class	Subclass	Date	Examiner
514	619	1/8/14	LS
514	535	1/8/14	LS
514	570	1/8/14	LS

INTERFERENCE SEARCHED			
Class	Subclass	Date	Examiner
514	**618**	**1/8/14**	**LS**

SEARCH NOTES (INCLUDING SEARCH STRATEGY)		
	DATE	EXMR
STIC (see 13535653); and npl	1/8/14	LS
odp:SAWA, SHIROU and FUJITA, SHUHEI	1/8/14	LS

UNITED STATES PATENT AND TRADEMARK OFFICE

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BIB DATA SHEET

CONFIRMATION NO. 1577

SERIAL NUMBER	FILING or 371(c) DATE RULE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
13/687,242	11/28/2012	514	1627	2012_5420

APPLICANTS

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INVENTORS

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

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

This application is a DIV of 13/353,653 01/19/2012 PAT 8497304
which is a DIV of 10/525,006 03/28/2005 PAT 8129431
which is a 371 of PCT/JP2004/000350 01/16/2004

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

JAPAN 2003-012427 01/21/2003

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

12/21/2012

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	30	3

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UNITED STATES

TITLE

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

FILING FEE RECEIVED		
2180	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

EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L5	218	BROMFENAC AND TYLOXAPOL	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2014/01/09 15:47
L6	41	L5 AND @PD<="20040116"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2014/01/09 15:48

1/9/2014 3:48:30 PM
C:\Users\lsoroush\Documents\EAST\Workspaces\1154715.wsp

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Named Inventor	:	Attorney Docket No. 2012-5420
Shirou SAWA	:	**Confirmation No. 1577**
Serial No. 13/687,242	:	Group Art Unit 1627
Filed November 28, 2012	:	Examiner Layla Soroush
AQUEOUS LIQUID PREPARATION CONTAINING 2-AMINO-3-(4-BROMOBENZOYL)PHENYLACETIC ACID	:	**Mail Stop: AMENDMENT**

INFORMATION DISCLOSURE STATEMENT

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

Sir/Madam:

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

1a. [] 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. [X] 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) [X] the fee of $180.00 ($90.00 for small entity) specified in 37 CFR 1.17(p) is enclosed.

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

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

the certification of paragraph 2 below is provided, and

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

2. It is hereby certified

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

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

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

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

b. [] an International Search Report submitted herewith,

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

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

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

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

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

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

Respectfully submitted,

/Warren M. Cheek, Jr./

Digitally signed by /Warren M. Cheek, Jr./
DN: cn=/Warren M. Cheek, Jr./, o, ou, email=wcheek@wenderoth.com, c=US
Date: 2014.01.15 11:54:14 -05'00'

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Facsimile (202) 721-8250
January 15, 2014

Sheet 1 of 1

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 15, 2014

ATTY DOCKET NO.	**SERIAL NO.**
2012-5420	13/687,242
FIRST NAMED INVENTOR	
Shirou SAWA	
FILING DATE	**GROUP**
November 28, 2012	1627

U.S. PATENT DOCUMENTS

*EXAMINER INITIAL		DOCUMENT NUMBER	DATE	NAME	CLASS	SUBCLASS	FILING DATE IF APPROPRIATE
	AA	4,910,225	3/1990	Ogawa et al.			
	AB	6,274,609	8/2001	Yasueda et al.			
	AC						
	AD						
	AE						
	AF						
	AG						
	AH						
	AI						

FOREIGN PATENT DOCUMENTS

		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION YES	TRANSLATION NO
	BA	0 306 984	3/1989	EP				
	BB							
	BC							
	BD							
	BE							

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

	CA	H. Scott et al., "Comparing the Surface Chemical Properties and the Effect of Salts on the Cloud Point of a Conventional Nonionic Surfactant, Octoxynol 9 (Triton X-100), and of its Oligomer, Tyloxapol (Triton WR-1339)", Journal of Colloid and Interface Science, Vol. 205, pp. 496-502, 1998.
	CB	
	CC	
	CD	

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.

(19) Europäisches Patentamt
European Patent Office
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(11) Publication number: **0 306 984 A1**

(12) EUROPEAN PATENT APPLICATION

(21) Application number: **88114804.3**

(51) Int. Cl.4: **A61K 9/06 , A61K 47/00**

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15.03.89 Bulletin 89/11

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(54) Preservative system forophthalmic formulations.

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

EP 0 306 984 A1

PRESERVATIVE SYSTEM FOR OPHTHALMIC FORMULATIONS

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

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

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

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

Organo-mercurials (e.g., thimerosal, phenylmercuric acetate and phenylmercuric nitrate) have been used extensively as the preservative in ophthalmic solutions. These compounds, however, pose difficulties due to potential mercury toxicity as well as poor chemical stability. Benzalkonium chloride, a quaternary ammonium compound, has been widely used in ophthalmic solutions, and is considered to be the preservative of choice. However, BAC has typically been considered to be incompatible with anionic drugs (e.g., salicylates or nitrates, etc.), forming insoluble complexes which cause the solution to become cloudy or turbid. Such a complex between the anionic drug and benzalkonium chloride can cause a decrease in the pharmaceutical activity of the anionic drug.

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

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

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

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

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

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

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

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

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

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

Definitions

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

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

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

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

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

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

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

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

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

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

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

Formulations

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

methods readily known to those skilled in the art.

Pharmaceutical ophthalmic formulations typically contain an effective amount, e.g., 0.001% to 10% wt/vol., preferably 0.002% to 5% wt/vol, most preferably 0.005% to 1% wt/vol of an active ingredient (e.g., the NSAID of the present invention). The amount of active ingredient will vary with the particular formulation and the disease state for which it is intended. The total concentration of solutes should be such that, if possible, the resulting solution is isotonic with the lacrimal fluid (though this is not absolutely necessary) and has a pH in the range of 6 to 8.

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

Ingredient	Amount
Active Agent	0.001% to 10.0% wt/vol.;
Preservative	0.001% to 1.0% wt/vol.;
Surfactant	0.001% to 1.0% wt/vol.;
Other Excipients	0% to 10.0% wt/vol.; and
Purified Water	q.s. to 100%.

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

Ingredient	Amount
Chelating agent	0.01% to 1.0%wt/vol.;
Tonicifier	q.s. to achieve isotonicity with lacrimal fluid; and
1N NaOH or 1N HCl	q.s. to adjust pH to 6.0 to 8.0.

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

Ingredient	Amount
NSAID	0.002% to 5.0% wt/vol.;
BAC (50% aq. soln.)	0.002% to 1.0% wt/vol.;
Octoxynol 40 (70% aq. soln.)	0.001% to 1.0% wt/vol.;
EDTA Na_2	0.01% to 1.0% wt/vol.;
NaCl	q.s. for isotonicity with lacrimal fluid;
1N NaOH or 1N HCl	q.s. to adjust pH to 7.4±0.4; and
Purified Water	q.s. to 100%.

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

Ingredient	Amount
NSAID	0.005% to 1.0% wt/vol.;
BAC (50% aq. soln.)	0.002% to 1.0% wt/vol.;
Octoxynol 40 (70% aq. soln.)	0.001% to 1.0% wt/vol.;
EDTA Na_2	0.01% to 1.0% wt/vol.;
NaCl	q.s. for isotonicity with lacrimal fluid;
1N NaOH or 1N HCl	q.s. to adjust pH to 7.4±0.4; and
Purified Water	q.s. to 100%.

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

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

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

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

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

The nonionic surfactants useful in the formulations of the present invention are preferably ethoxylated octylphenol compounds, such as octylphenoxypoly-(ethyleneoxy)ethanols, more preferably, a homologous series of surfactants sold under the trade name Igepal CA with a numerical suffix indicating the mole ratio of ethylene oxide to octylphenol, the ratio being 3 to 40. Examples include Octoxynol 9, Octoxynol 12, Octoxynol 13, and Octoxynol 40, and most preferably Octoxynol 40, manufactured and sold by GAF under the trade name Igepal CA897 (a 70% aqueous solution of Octoxynol 40).

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

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

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

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

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

These formulations are prepared by dissolving the solutes (e.g., the NSAID, the preservative, the surfactant, the chelating agent, and the buffering agent) in a suitable quantity of water, adjusting the pH to about 6 to 8, preferably 6.8 to 8.0 and most preferably 7.4, making a final volume adjustment to 100% with additional water, and sterilizing the preparation using any suitable method known to those in the art.

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

Preferred Formulations

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

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

The preferred preservative of the invention is benzalkonium chloride.

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

chloride as the preservative.

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

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

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

Ingredient	Amount
NSAID	0.002% to 5.0% wt/vol.;
BAC (50% aq. soln.)	0.002% to 1.0% wt/vol.;
Octoxynol 40 (70% aq. soln.)	0.001% to 1.0% wt/vol.;
EDTA Na_2	0.01% to 1.0% wt/vol.;
NaCl	q.s. for isotonicity with lacrimal fluid;
1N NaOH or 1N HCl	q.s. to adjust pH to 7.4±0.4; and
Purified Water	q.s. to 100%.

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

Ingredient	Amount
NSAID	0.005% to 1.0% wt/vol.;
BAC (50% aq. soln.)	0.002% to 1.0% wt/vol.;
Octoxynol 40 (70% aq. soln.)	0.001% to 1.0% wt/vol.;
EDTA Na_2	0.01% to 1.0% wt/vol.;
NaCl	q.s. for isotonicity with lacrimal fluid;
1N NaOH or 1N HCl	q.s. to adjust pH to 7.4±0.4; and
Purified Water	q.s. to 100%.

A preferred ophthalmic NSAID solution has the following formulation:

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

Most preferred is the ophthalmic solution according to the above formulation wherein the NSAID is Ketorolac Tromethamine or an isomer thereof.

Utility and Administration

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

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

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

suspensions or ointments, or by subconjunctival injection.

The dosage level will, of course, depend on the concentration of the drops, the condition of the subject and the individual magnitude of responses to treatment. However, typical dosage ranges might be about 2 to 10 drops of 0.5% solution of active ingredient per day.

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

Testing

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

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

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

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

EXAMPLE 1

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

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

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

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

EXAMPLE 2

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

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

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

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

EXAMPLE 3

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

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

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

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

EXAMPLE 4

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

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

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

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

EXAMPLE 5

Physical stability of the formulations of the present invention is measured by preparing clear formulations, in the concentrations shown in the table below, sealing them in sterilized containers, and observing the clarity of the solution after a period of one month and again after five months. Solutions that remain clear are considered stable in this procedure.

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

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

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

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

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

EXAMPLE 6

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

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

EXAMPLE 7

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

Ophthalmic examinations were performed preoperatively (within 3 weeks of surgery) and during the first

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

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

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

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

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

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

129 patients began treatment for 21 days with either ketorolac or vehicle. In this study, the ketorolac formulation used was that illustrated in Example 1 above. During the first week 118 patients and during the second week 110 patients were evaluated for postoperative inflammation with ophthalmic examinations and fluorophotometry. During the third week, 83 patients were evaluated with ophthalmic examinations alone. At 2 weeks ketorolac provide significantly greater anti-inflammatory activity than the vehicle as measured by fluorophotometry ($p = 0.019$). When patients were excluded who had greater than 40% difference in fluorescein concentration between eyes at baseline, the p-value during week 2 rose to 0.06. In addition, the vehicle-treated patients had more ocular inflammation seen on slit lamp examination, e.g., eyelid edema ($p = 0.001$), conjunctival injection ($p = 0.001$), and Descemet folds ($p = 0.002$) than did the ketorolac-treated patients. Finally, there were significantly more complaints ($p = 0.01$) and more sever complaints consistent with ocular inflammation (photophobia, iritis, conjunctival injection) in the vehicle-treated group than in the ketorolac-treated group.

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

EXAMPLE 8

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

Thirty patients with allergic conjunctivitis participated in the study. Following admission to the study, patients reported to the investigator for baseline, mid-week, and final one-week examinations. At each of these visits, patients received ophthalmic examinations (visual acuity, external eye exam using slit lamp biomicroscopy, measurement of intraocular pressure, and undilated ophthalmoscopic examination). Laboratory tests included a conjunctival scraping performed at baseline and the final exam.

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

Fisher's Exact Test. two-tailed).

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

EXAMPLE 9

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

EXAMPLE 10

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

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

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

Claims

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

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

3. The ophthalmic NSAID formulation of any one of Claims 1 and 2 wherein said nonionic ethoxylated octylphenol surfactant is an octylphenoxypoly(ethyleneoxy)-ethanol with a mole ratio of ethylene oxide to octylphenol of between 3:1 and 40:1.

4. The ophthalmic NSAID formulation of any one of Claims 1 to 3 wherein said nonionic ethoxylated octylphenol surfactant is Octoxynol 40.

5. The ophthalmic NSAID formulation of any one of Claims 1 to 4 including disodium edetate.

6. The ophthalmic NSAID formulation of any one of Claims 1 to 5 wherein said NSAID is selected from the group: ketorolac, indomethacin, flurbiprofen, and diclofenac, or their isomers, pharmaceutically acceptable salts, or esters.

7. The ophthalmic NSAID formulation of any one of Claims 1 to 6 wherein said NSAID is Ketorolac Tromethamine.

8. The ophthalmic NSAID formulation of any one of Claims 1 to 6 wherein said NSAID is the (1)-isomer of ketorolac or one of its pharmaceutically acceptable salts.

9. The ophthalmic NSAID formulation of any one of Claims 1 to 8 comprising:

NSAID 0.001% to 10.0% wt/vol.;

Preservative 0.001% to 1.0% wt/vol.;

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

10. The ophthalmic NSAID formulation of Claim 9 including:
Chelating agent 0.01% to 1.0%wt/vol.;
Tonicifier q.s. to achieve isotonicity with lacrimal fluid; and
1N NaOH or 1N HCl q.s. to adjust pH to 6.0 to 8.0.

11. The ophthalmic NSAID formulation of Claim 10 comprising:
NSAID 0.50% wt/vol.;
BAC(50% aq. soln.) 0.02% wt/vol.;
Octoxynol 40 (70% aq. soln.) 0.01% wt/vol.;
EDTA Na_2 0.10% wt/vol.;
NaCl 0.79% wt/vol.;
1N NaOH or 1N HCl q.s. to adjust pH to 7.4±0.4; and
Purified Water q.s. to 100%.

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

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

14. The preservative system of Claim 13 wherein said preservative is benzalkonium chloride and said surfactant is Octoxynol 40.

15. The use of a formulation of any one of Claims 1 to 12 for the manufacture of a medicament for the treatment or prevention of ophthalmic diseases, particularly ocular inflammatory diseases.

16. The use of a preservative system of any one of Claims 13 and 14 for manufacture of a medicament for the treatment or prevention of ophthalmic diseases, particularly ocular inflammatory diseases.

17. A process for the preparation of an ophthalmic NSAID formulation which comprises mixing
0.001% to 10.0% wt/vol. of an NSAID,
0.001% to 1.0% wt/vol. of a preservative,
0.001% to 1.0% wt/vol. of a nonionic ethoxylated octylphenol surfactant, and
Purified Water q.s. to 100%.

18. The process of Claim 17 which further comprises mixing
0.01% to 1.0%wt/vol. of a chelating agent,
q.s. of a tonicifier to achieve isotonicity with lacrimal fluid, and
q.s. of 1N NaOH or 1N HCl to adjust pH to 6.0 to 8.0.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number

EP 88 11 4804

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.4)
Y	DE-A-3 026 402 (SYNTEX) * Claims; page 9, line 31; page 10, lines 15-19 *	1-7,9-16	A 61 K 9/06 A 61 K 47/00
Y	US-A-4 087 538 (J.B. PORTNOFF) * Claims; column 2, lines 34-36,47-51; column 3, lines 36-40,53 *	1-7,9-16	
Y	CHEMICAL ABSTRACTS, vol. 88, no. 25, 19th June 1978, page 166, no. 183735c, Columbus, Ohio, US; M.T. NADIR et al.: "Influence of (ethoxy)5 octyl phenon on the antibacterial properties of preservatives", & J. PHARM. PHARMACOL. 1977, 29(SUPPL., BR. PHARM. CONF. 1977), 67P * Abstract *	1-7,9-16	
A	WO-A-8 504 106 (J. CORBIERE) * Claims 1-2,5,7 *	1-7,9-16	

TECHNICAL FIELDS SEARCHED (Int. Cl.4)

A 61 K

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	23-11-1988	SCARPONI U.

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

EPO FORM 1503 03.82 (P0401)

Electronic Patent Application Fee Transmittal

Application Number:	13687242
Filing Date:	28-Nov-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_5420

Filed as Large Entity

Utility under 35 USC 111(a) Filing Fees

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

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
Submission- Information Disclosure Stmt	1806	1	180	180
		Total in USD ($)		**180**

Electronic Acknowledgement Receipt

EFS ID:	17917590
Application Number:	13687242
International Application Number:	
Confirmation Number:	1577
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_5420
Receipt Date:	15-JAN-2014
Filing Date:	28-NOV-2012
Time Stamp:	15:54:30
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Credit Card
Payment was successfully received in RAM	$180
RAM confirmation Number	2371
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)

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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	Information Disclosure Statement (IDS) Form (SB08)	AttachZ1_Ids.pdf	186220 584bbfddc07ed7c54f7eb64d9ddc81c51a2778a3	no	3
Warnings:					
Information:					
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.					
This is not an USPTO supplied IDS fillable form					
2	Information Disclosure Statement (IDS) Form (SB08)	AttachZ2_SB08.pdf	120279 e5c006c5345dbf35dfab9f384b8ee9d4b6220ce9	no	1
Warnings:					
Information:					
This is not an USPTO supplied IDS fillable form					
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.					
3	Foreign Reference	AttachZBA.pdf	775776 d14702bcaa080ba72fd9c466b88870f4d459d208	no	13
Warnings:					
Information:					
4	Non Patent Literature	AttachZCA.pdf	4779724 acd56775ad00351d84f658fec748de5ac3c33eb9	no	7
Warnings:					
Information:					
5	Fee Worksheet (SB06)	fee-info.pdf	30954 36750bc43dcfa135edc24feba342ceebb459a38e	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	5892953		

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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.

Application Number	Application/Control No.	Applicant(s)/Patent under Reexamination	
	13/687,242	SAWA ET AL.	

Document Code - DISQ	Internal Document – DO NOT MAIL

TERMINAL DISCLAIMER	☒ APPROVED	☐ DISAPPROVED
Date Filed : 10/22/13	This patent is subject to a Terminal Disclaimer	

Approved/Disapproved by:

ANDRE ROBINSON

3 TDS WERE APPRVD.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Named Inventor	:	Attorney Docket No. 2012-5420
Shirou SAWA	:	**Confirmation No. 1577**
Serial No. 13/687,242	:	Group Art Unit 1627
Filed November 28, 2012	:	Examiner Layla Soroush
AQUEOUS LIQUID PREPARATION CONTAINING 2-AMINO-3-(4-BROMOBENZOYL)PHENYLACETIC ACID	:	**Mail Stop: AMENDMENT**

TERMINAL DISCLAIMER UNDER 37 CFR 1.321

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

Sir/Madam:

The owner, SENJU PHARMACEUTICAL CO., LTD., of 100% interest in the instant application, hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application, which would extend beyond the expiration date of the full statutory term defined in 35 USC 154 and 173 as shortened by any terminal disclaimer filed prior to the grant of any patent granted on pending second Application Number 13/353,653, filed January 19, 2012. The owner hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and any patent granted on the second application are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon grantee, its successors or assigns.

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

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

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

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

[X] The undersigned is an attorney of record.

October 22, 2013

/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: 2013.10.22 15:49:49 -04'00'

Warren M. Cheek
Reg. No. 33,367

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

WMC/dlk
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Electronic Patent Application Fee Transmittal

Application Number:	13687242
Filing Date:	28-Nov-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_5420

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:				
Statutory or Terminal Disclaimer	1814	3	160	480
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
			Total in USD ($)	**480**

Electronic Acknowledgement Receipt

EFS ID:	17196235
Application Number:	13687242
International Application Number:	
Confirmation Number:	1577
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_5420
Receipt Date:	22-OCT-2013
Filing Date:	28-NOV-2012
Time Stamp:	17:27:38
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Credit Card
Payment was successfully received in RAM	$480
RAM confirmation Number	7170
Deposit Account	230975
Authorized User	CHEEK JR., WARREN M.

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Charge any Additional Fees required under 37 C.F.R. Section 1.17 (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_Amdt.pdf	237015 f3f46b3a419a2766adf4cbde8f0462187fc9acd9	yes	14

Multipart Description/PDF files in .zip description

Document Description	Start	End
Amendment/Req. Reconsideration-After Non-Final Reject	1	1
Claims	2	8
Applicant Arguments/Remarks Made in an Amendment	9	14

Warnings:

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Information:

2	Terminal Disclaimer Filed	AttachB.pdf	142287 19c49ed1cda456b081f1cf23635d50dc34f2f578	no	2

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3	Terminal Disclaimer Filed	AttachC.pdf	141923 161ffd1e41d18b930712e2b36ea94df784422942	no	2

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Information:

4	Terminal Disclaimer Filed	AttachD.pdf	146257 77a969aa3a1d342d25d820cbfd6083a263016f22	no	2

Warnings:

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Information:

5	Fee Worksheet (SB06)	fee-info.pdf	30850 9d76e273e2b189f48fe4016ac8ccfcbc4b1da08d	no	2

Warnings:	
Information:	
Total Files Size (in bytes):	698332

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New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

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

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

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of	:	Attorney Docket No. 2012_5420
Shirou SAWA et al.	:	Confirmation No. 1577
Serial No. 13/687,242	:	Group Art Unit 1627
Filed November 28, 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 1, 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

1-18. (Canceled)

19. (Currently amended) A stable aqueous liquid preparation comprising: (a) a first component; and (b) a second component; wherein the first component is 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof, wherein the hydrate is at least one selected from a 1/2 hydrate, 1 hydrate, and 3/2 hydrate; the first component is the sole pharmaceutical active ingredient contained in the preparation; the second component is tyloxapol and is present in said liquid preparation in an amount sufficient to stabilize said first component; and wherein said stable liquid preparation is formulated for ophthalmic administration.

20. (Previously presented) The aqueous liquid preparation according to claim 19, further comprising a quaternary ammonium salt.

21. (Previously presented) The aqueous liquid preparation according to claim 19, wherein the first component is a 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt.

22. (Previously presented) The aqueous liquid preparation according to claim 19, wherein the concentration of tyloxapol is from about 0.01 w/v % to about 0.05 w/v %; and wherein the first component is a 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt, wherein the concentration of the 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt is from about 0.01 to about 0.2 w/v %.

23. (Previously presented) The aqueous liquid preparation according to claim 22, wherein the concentration of the 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt is about 0.1 w/v %.

24. (Previously presented) The aqueous liquid preparation according to claim 19, wherein the pH is from about 7.5 to about 8.5.

25. (Currently amended) The stable aqueous liquid preparation of claim 19, wherein the stable aqueous liquid preparation consists essentially of: (a) 2-amino-3-(4- bromobenzoyl)phenylacetic acid sodium salt, (b) tyloxapol, (c) boric acid, (d) sodium tetraborate, (e) EDTA sodium salt, (f) benzalkonium chloride, (g) polyvinylpyrrolidone, and (h) sodium sulfite, wherein said liquid preparation is formulated for ophthalmic administration, and wherein the concentration of the 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt is from about 0.02 w/v% to about 0.1 w/v %.

26. (Previously presented) A stable aqueous liquid preparation comprising: (a) a first component; and (b) a second component; wherein the first component is 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof, wherein the hydrate is at least one selected from a 1/2 hydrate, 1 hydrate, and 3/2 hydrate; the second component is tyloxapol; wherein said stable liquid preparation is formulated for ophthalmic administration; and wherein the stable aqueous liquid preparation is characterized in that greater than about 90% of the original amount of the first component remains in the preparation after storage at about 60 °C for 4 weeks.

27. (Currently amended) The aqueous liquid preparation according to claim 26, further comprising a quaternary ammonium salt, and wherein the first component is the sole pharmaceutical active ingredient contained in the preparation.

28. (Previously presented) The stable aqueous liquid preparation of claim 26, wherein the stable aqueous liquid preparation is characterized in that greater than about 92% of the original amount of the first component remains in the preparation after storage at about 60 °C for 4 weeks.

29. (Previously presented) The aqueous liquid preparation according to claim 26, wherein the concentration of tyloxapol is from about 0.01 w/v % to about 0.05 w/v %; and wherein the first component is a 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt, wherein the

concentration of the 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt is from about 0.01 to about 0.2 w/v %.

30. (Previously presented) The aqueous liquid preparation according to claim 29, wherein the pH is from about 7.5 to about 8.5.

31. (Previously presented) The stable aqueous liquid preparation of claim 26, wherein the stable aqueous liquid preparation consists essentially of: (a) 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof, wherein the hydrate is at least one selected from a 1/2 hydrate, 1 hydrate, and 3/2 hydrate; (b) tyloxapol; (c) boric acid; (d) sodium tetraborate; (e) EDTA sodium salt; (f) benzalkonium chloride; (g) polyvinylpyrrolidone; and (h) sodium sulfite; and wherein the concentration of the 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt is from about 0.02 w/v% to about 0.1 w/v %.

32. (Currently amended) A stable aqueous liquid preparation comprising: (a) a first component; and (b) a second component; wherein the first component is 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof, wherein the hydrate is at least one selected from a 1/2 hydrate, 1 hydrate, and 3/2 hydrate; the first component is the sole pharmaceutical active ingredient contained in the preparation; the second component is tyloxapol; wherein said stable liquid preparation is formulated for ophthalmic administration; provided that the liquid preparation does not include mannitol.

33. (Previously presented) The aqueous liquid preparation according to claim 32, further comprising a quaternary ammonium salt.

34. (Previously presented) The aqueous liquid preparation according to claim 32, wherein the first component is a 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt.

35. (Previously presented) The aqueous liquid preparation according to claim 34, wherein the concentration of tyloxapol is from about 0.01 w/v % to about 0.05 w/v % and the concentration of the 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt is from about 0.05 to about 0.2 w/v %.

36. (Previously presented) The aqueous liquid preparation according to claim 35, wherein the pH is from about 7.5 to about 8.5.

37. (Previously presented) The stable aqueous liquid preparation of claim 32; wherein the stable aqueous liquid preparation consists essentially of: (a) 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof, wherein the hydrate is at least one selected from a 1/2 hydrate, 1 hydrate, and 3/2 hydrate; (b) tyloxapol; (c) boric acid; (d) sodium tetraborate; (e) EDTA sodium salt; (f) benzalkonium chloride; (g) polyvinylpyrrolidone; and (h) sodium sulfite; wherein the concentration of the 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt is from about 0.02 w/v% to about 0.1 w/v %.

38. (Previously presented) The stable aqueous liquid preparation of claim 32, wherein the stable aqueous liquid preparation is characterized in that greater than about 90% of the original amount of the first component remains in the preparation after storage at about 60 °C for 4 weeks.

39. (Previously presented) The aqueous liquid preparation according to claim 38, further comprising a quaternary ammonium salt.

40. (Previously presented) The stable aqueous liquid preparation of claim 38; wherein the stable aqueous liquid preparation is characterized in that greater than about 92% of the original amount of the first component remains in the preparation after storage at about 60 °C for 4 weeks.

41. (Previously presented) The aqueous liquid preparation according to claim 38, wherein the concentration of tyloxapol is from about 0.01 w/v % to about 0.05 w/v %; and wherein the first component is a 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt, wherein the concentration of the 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt is from about 0.01 to about 0.2 w/v %.

42. (Previously presented) The aqueous liquid preparation according to claim 41, wherein the pH is from about 7.5 to about 8.5.

43. (Previously presented) The stable aqueous liquid preparation of claim 38, wherein the stable aqueous liquid preparation consists essentially of: (a) 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof, wherein the hydrate is at least one selected from a 1/2 hydrate, 1 hydrate, and 3/2 hydrate; (b) tyloxapol; (c) boric acid; (d) sodium tetraborate; (e) EDTA sodium salt; (f) benzalkonium chloride; (g) polyvinylpyrrolidone; and (h) sodium sulfite; wherein said liquid preparation is formulated for ophthalmic administration; and wherein the concentration of the 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt is from about 0.02 w/v% to about 0.1 w/v %.

44. (Currently amended) The aqueous liquid preparation of claim 19, wherein the aqueous liquid preparation further satisfies the preservative efficacy standard of EP-criteria B of the European Pharmacopoeia as follows:

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; and

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.

45. (Currently amended) The aqueous liquid preparation of claim 26, wherein the aqueous liquid preparation further satisfies the preservative efficacy standard of EP-criteria B of the European Pharmacopoeia as follows:

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; and

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.

46. (Currently amended) The aqueous liquid preparation of claim 32, wherein the aqueous liquid preparation further satisfies the preservative efficacy standard of EP-criteria B of the European Pharmacopoeia as follows:

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; and

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.

47. (Currently amended) The aqueous liquid preparation of claim 38, wherein the aqueous liquid preparation further satisfies the preservative efficacy standard of EP-criteria B of the European Pharmacopoeia as follows:

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; and

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.

48. (Currently amended) The aqueous liquid preparation of claim 40, wherein the aqueous liquid preparation further satisfies the preservative efficacy standard of EP-criteria B of the European Pharmacopoeia as follows:

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; and

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.

REMARKS

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

Applicants express their sincere appreciation to the Examiner for her courtesy and helpful assistance provided to the Applicants' undersigned representative and representative Dr. Toan Vo during the telephone interview held on September 18, 2013.

The foregoing amendments are presented according to the discussion with the Examiner, and for the reasons discussed during the interview, are believed to overcome all grounds of rejection.

I. INFORMALITIES

In item 5 and 7 of the Office Action summary page, it is respectfully requested that the pending claims be corrected to claims 19-48.

In item 12 of the Office Action summary page, it is respectfully requested that the claim of foreign priority be acknowledged, and receipt of the certified copy of the priority document be acknowledged, which copy is present in the Image File Wrapper.

II. SUPPORT FOR AMENDED CLAIMS

Claims 19, 27 and 32 are amended to specify that "the first component is the sole pharmaceutical active ingredient contained in the preparation;". This amendment is supported by page 7 (lines 14-17) and page 13 (lines 11-13) of the specification, which teaches that the claimed preparation may be prepared with 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof (hereinafter "bromfenac"), and with "other same or different kind of active ingredients" so long as the purpose of the present invention is achieved. Thus, a preparation containing bromfenac as the sole active ingredient is clearly taught by the specification.

The amendment is further supported by the Examples of the specification which teach compositions having bromfenac as the sole pharmaceutical active ingredient contained in the preparation. The first specific composition taught in the specification is found in Experimental Example 1 (pages 14-15). The sole pharmaceutical active ingredient contained in the preparation is Sodium 2-amino-3-(4-bromobenzoyl)phenylacetate, i.e. bromfenac.

The second specific composition taught in the specification is found in Experimental Example 2 (pages 16-18). The sole pharmaceutical active ingredient contained in the preparation is Sodium 2-amino-3-(4-bromobenzoyl)phenylacetate, i.e. bromfenac.

The third specific composition taught in the specification is found in Example 1 (page 21). The sole pharmaceutical active ingredient contained in the preparation is Sodium 2-amino-3-(4-bromobenzoyl)phenylacetate 3/2 hydrate, i.e. bromfenac.

The fourth specific composition taught in the specification is found in Example 2 (page 22). The sole pharmaceutical active ingredient contained in the preparation is Sodium 2-amino-3-(4-bromobenzoyl)phenylacetate 3/2 hydrate, i.e. bromfenac.

The fifth and final specific composition taught in the specification is found in Example 3 (page 23). The sole pharmaceutical active ingredient contained in the preparation is Sodium 2-amino-3-(4-bromobenzoyl)phenylacetate 3/2 hydrate, i.e. bromfenac.

In summary, a preparation containing bromfenac as the sole active ingredient is clearly taught by the specification. Thus, the amendment to claims 19, 27 and 32 is clearly supported by the specification.

A minor error has been corrected in claim 25 which is evident from claim 31.

Claims 44-48 are amended to specify the preservative efficacy standard of EP-criteria B of the European Pharmacopoeia, which is explicitly supported on page 20, last line, to page 21 of the specification. Thus, the claims are amended to recite "as follows:

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; and

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".

III. REJECTION OF CLAIMS 44-48 UNDER 35 U.S.C. 112

Claims 44-48 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for the recitation of the standard of EP-criteria B of the European Pharmacopoeia.

This ground of rejection is deemed to be overcome by the foregoing amendments.

IV. REJECTION OF CLAIMS 19, 21-24, 26, 28-30, 32, 34-36, 38, 40-42 and 44-48 UNDER 35 U.S.C. § 103(a) BASED UPON GAMACHE

A. Claims 19, 21-24, 32, 34-36, 38, 40-42, 44 and 46-48

Claims 19, 27 and 32 now recite that the preparation comprises the first component, 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof (i.e. "bromfenac"), as the sole pharmaceutical active ingredient contained in the preparation.

Gamache does not teach or suggest any preparation comprising bromfenac as the sole pharmaceutical active ingredient.

Gamache teaches only compositions that must contain 5-HT1D and/or 5-HT1B receptor agonists. Gamache's compositions may contain additional pharmaceutical active ingredients. Gamache does not teach or suggest any composition comprising bromfenac as the sole pharmaceutical active ingredient.

Thus, Gamache does not teach or suggest claims 19, 27 or 32 as amended. Accordingly, Gamache fails to teach or suggest claims 21-24, 34-36, 38, 40-42, 44 and 46-48 which are dependent upon claims 19 and 32.

Consequently, Gamache does not render these claims obvious.

B. Claims 26, 28-30 and 45

Claim 26 recites that "said stable liquid preparation is formulated for ophthalmic administration; and wherein the stable aqueous liquid preparation is characterized in that greater than about 90% of the original amount of the first component remains in the preparation after storage at about 60 °C for 4 weeks."

Gamache does not teach or suggest any preparation comprising bromfenac and tyloxapol, wherein greater than 90% of the original amount of bromfenac remains after storage at 60 °C for 4 weeks.

Gamache disclosed generally that anti-inflammatory drugs, such as bromfenac or others, may be used in a composition including any surfactants "known to those skilled in the art," including polysorbate 80. However, Gamache did not recognize the problem that bromfenac degrades rapidly in the presence of polysorbate 80, a surfactant "known to those skilled in the

art" (according to Gamache), as Applicant demonstrated in the grandparent application Serial No. 10/525,006.

Applicant recognized this problem and surprisingly found that the degradation of bromfenac could be avoided by specifically including tyloxapol in the preparation.

Thus, the preparation of claim 26, and its dependent claims, are not obvious from Gamache.

V. REJECTION OF CLAIMS 20, 27, 33, and 39 UNDER 35 U.S.C. § 103(a) OVER GAMACHE IN VIEW OF DESAI

Claim 20 is dependent upon independent claim 19. As pointed out above, claim 19 is nonobvious over Gamache because Gamache does not teach or suggest any composition wherein bromefenac is the sole pharmaceutical active ingredient. Therefore, adding Desai to show the use of benzalkonium chloride still does not overcome the deficiency of Gamache. Therefore, claim 20 is nonobvious over Gamache in view of Desai.

Claim 27 is amended to recite that bromfenac is the sole pharmaceutical active ingredient in the preparation. As pointed out above, claim 27 is nonobvious over Gamache because Gamache does not teach or suggest any composition wherein bromefenac is the sole pharmaceutical active ingredient. Therefore, adding Desai to show the use of benzalkonium chloride still does not overcome the deficiency of Gamache. Therefore, claim 27 is nonobvious over Gamache in view of Desai.

Claims 33 and 39 are dependent upon independent claim 32. As pointed out above, claim 32 is nonobvious over Gamache because Gamache does not teach or suggest any composition wherein bromfenac is the sole pharmaceutical active ingredient. Therefore, adding Desai to show the use of benzalkonium chloride still does not overcome the deficiency of Gamache. Moreover, all Desai's experiments include mannitol, which is excluded from the compositions of present claims 33 and 39. Therefore, the combination of Gamache and Desai does not teach or suggest any composition wherein bromfenac is the sole pharmaceutical active ingredient and wherein mannitol is excluded. Consequently, claims 33 and 39 are nonobvious over Gamache in view of Desai.

VI. REJECTION OF CLAIMS 25, 31, 37 AND 43 UNDER 35 U.S.C. § 103(a) OVER GAMACHE IN VIEW OF OGAWA AND DE BRUIJU

Claim 25 is dependent upon independent claim 19. As pointed out above, claim 19 is nonobvious over Gamache because Gamache does not teach or suggest any composition wherein bromefenac is the sole pharmaceutical active ingredient. Therefore, adding Ogawa and De Bruiju to show the use of sodium tetraborate, sodium sulfite, polyvinylpyrrolidone and boric acid does not overcome the deficiency of Gamache. Therefore, claim 25 is nonobvious over Gamache in view of Ogawa and De Bruiju.

Claim 31 is dependent upon independent claim 26. As pointed out above, claim 26 is nonobvious over Gamache because Gamache does not teach or suggest any preparation comprising bromfenac and tyloxapol, wherein greater than 90% of the original amount of bromfenac remains after storage at 60 °C for 4 weeks. Therefore, adding Ogawa and De Bruiju to show the use of sodium tetraborate, sodium sulfite, polyvinylpyrrolidone and boric acid does not overcome the deficiency of Gamache. Therefore, claim 31 is nonobvious over Gamache in view of Ogawa and De Bruiju.

Claim 37 is dependent upon independent claim 32. As pointed out above, claim 32 is nonobvious over Gamache because Gamache does not teach or suggest any composition wherein bromefenac is the sole pharmaceutical active ingredient. Therefore, adding Ogawa and De Bruiju to show the use of sodium tetraborate, sodium sulfite, polyvinylpyrrolidone and boric acid does not overcome the deficiency of Gamache. Therefore, claim 37 is nonobvious over Gamache in view of Ogawa and De Bruiju.

Claim 43 is dependent upon independent claim 32. As pointed out above, claim 32 is nonobvious over Gamache because Gamache does not teach or suggest any composition wherein bromefenac is the sole pharmaceutical active ingredient. Therefore, adding Ogawa and De Bruiju to show the use of sodium tetraborate, sodium sulfite, polyvinylpyrrolidone and boric acid does not overcome the deficiency of Gamache. Therefore, claim 43 is nonobvious over Gamache in view of Ogawa and De Bruiju.

VII. DOUBLE PATENTING REJECTIONS

All claims are rejected on the ground of nonstatutory double patenting as being unpatentable over claims of U.S. Patent No. 7,829,544, U.S. Patent No. 8,129,431, U.S. Serial No. 11/755,662 and U.S. Serial No. 13/353,653.

A. U.S. Patent No. 7,829,544, U.S. Patent No. 8,129,431, and U.S. Serial No. 13/353,653

Without acquiescing to the grounds of rejection, there are submitted herewith a Terminal Disclaimer over U.S. Patent No. 7,829,544, U.S. Patent No. 8,129,431, and U.S. Serial No. 13/353,653.

B. U.S. Serial No. 11/755,662

Regarding the provisional double patenting rejection over U.S. Serial No. 11/755,662, the rejection is deemed to be overcome by the submission of a Letter of Express Abandonment filed in the '662 application by the attorney of record on October 18, 2013 and the undersigned representative on October 22, 2013.

Accordingly, the double patenting grounds of rejection are deemed to be overcome.

VIII. CONCLUSION

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

Applicant respectfully submits that claims 19-48 are patentable over the prior art. A favorable action on the merits is solicited.

Respectfully submitted,

/Warren M. Cheek, Jr./

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October 22, 2013

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Named Inventor	:	Attorney Docket No. 2012-5420
Shirou SAWA	:	**Confirmation No. 1577**
Serial No. 13/687,242	:	Group Art Unit 1627
Filed November 28, 2012	:	Examiner Layla Soroush
AQUEOUS LIQUID PREPARATION CONTAINING 2-AMINO-3-(4-BROMOBENZOYL)PHENYLACETIC ACID	:	**Mail Stop: AMENDMENT**

TERMINAL DISCLAIMER UNDER 37 CFR 1.321

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

Sir/Madam:

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

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

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

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

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

[X] The undersigned is an attorney of record.

/Warren M. Cheek, Jr./

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October 22, 2013

Warren M. Cheek
Reg. No. 33,367

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

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Named Inventor	:	Attorney Docket No. 2012-5420
Shirou SAWA	:	**Confirmation No. 1577**
Serial No. 13/687,242	:	Group Art Unit 1627
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Sir/Madam:

The owner, SENJU PHARMACEUTICAL CO., LTD., of 100% interest in the instant application, hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application, which would extend beyond the expiration date of the full statutory term defined in 35 USC 154 and 173, as shortened by any terminal disclaimer, of prior Patent No. 7,829,544, issued November 9, 2010. The owner hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and the prior patent are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors or assigns.

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

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

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

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

[X] The undersigned is an attorney of record.

/Warren M. Cheek, Jr./

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

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PTO/SB/06 (09-11)
Approved for use through 1/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 13/687,242	Filing Date 11/28/2012	☐ To be Mailed

ENTITY: ☒ LARGE ☐ SMALL ☐ MICRO

APPLICATION AS FILED – PART I

	(Column 1)	(Column 2)		
FOR	NUMBER FILED	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

		(Column 1)		(Column 2)	(Column 3)		
AMENDMENT	10/22/2013	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 30	Minus	** 30	= 0	X $80 =	0
	Independent (37 CFR 1.16(h))	* 3	Minus	***3	= 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

		(Column 1)		(Column 2)	(Column 3)		
AMENDMENT		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	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
/GAIL WOOTEN/

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/687,242	11/28/2012	Shirou SAWA	2012_5420	1577

513 7590 08/01/2013

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EXAMINER	
SOROUSH, LAYLA	

ART UNIT	PAPER NUMBER
1627	

NOTIFICATION DATE	DELIVERY MODE
08/01/2013	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. 13/687,242	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 *9 April 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) *29-48* 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) *29-48* 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.

Attachment(s)

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

2) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/28/12*.

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 April 9, 2013 to the restriction requirement made on March 25, 2013.

Applicant's election of benzalkonium chloride as the species of quarternary ammonium salts is hereby acknowledged. . Because 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)).

Claims 19-48 read on the elected species.

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

Claim Rejections - 35 USC § 112

The following is a quotation of 35 U.S.C. 112(b):
(b) CONCLUSION.—The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the inventor or a joint inventor regards as the invention.

The following is a quotation of 35 U.S.C. 112 (pre-AIA), second paragraph:
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.

Claims 44-48 rejected under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the inventor or a joint inventor, or for pre-AIA the applicant regards as the invention. Applicant has claimed the preservative efficacy standard is satisfied by EP-criteria B of the European Pharmacopoeia. Where possible, claims are to be complete in themselves. Incorporation by reference to a specific figure or table "is permitted only in exceptional circumstances where there is no practical way to define the invention in words and where it is more concise to incorporate by reference than duplicating a drawing or table into the claim. Incorporation by reference is a

necessity doctrine, not for applicant's convenience." Ex parte Fressola, 27 USPQ2d 1608, 1609 (Bd. Pat. App. & Inter. 1993) (citations omitted).

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 19, 21-24, 26, 28-30, 32, 34-36, 38, 40-42, and 44-48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gamache, et al. (WO 01/15677 A2; 03/2001).

Gamache teaches compositions for otic and intranasal use (p.6, lines 5-6) that contain a combination of a 5-HT agonist and an anti-inflammatory agent (p. 6, lines 1-4; p. 12 lines 9-10) or alternatively sequential or concurrent dosing of separate compositions that contain the 5-HT antagonist in one composition and the anti-inflammatory agent in a second composition (p. 12, lines 9-11); specifically claimed is the anti-inflammatory specie bromfenac (2-amino-3-(4-bromobenzoyl)phenylacetic acid). Typical concentrations of anti-inflammatory agents, such as bromfenac, are taught in the range 0.01-1.0 % (w/v) (overlapping with 0.01-0.5; p. 13, lines 6-8); aqueous formulations are preferred (p. 10, lines 11-14); tyloxapol is taught in a concentration of 0.05 % (w/v) (p. 16, line 30). The salt form of bromfenac in solution will be the same when the acid is dissolved in a solution followed by adjustment to the desired pH with NaOH/HCl (Gamache, p. 15, line 33) as when the sodium salt is dissolved in solution adjusted to the same pH; in this case Gamache also teaches the sodium salt limitation of instant claim 21. The concentration range of 0.01-1.0% overlaps and encompasses the claimed concentration range of the sodium salt of bromfenac instantly claimed.

Although, the reference does not exemplify an aqueous liquid preparation comprising the first component and second component, it would have been obvious

for one of ordinary skill in the art at the time of the invention to select concentrations of bromfenac in the invention of Gamache. It would have been obvious to adjust the concentration of tyloxapol, to see what the effect would be on the solubility and stability of the aqueous preparations, which would have resulted in the effective concentrations of the instant claims. It would also have been obvious to adjust the pH to values in the 7.5 to 8.5 range, with the potential of dissolving and/or stabilizing more of the acidic drug, bromfenac, in a more aqueous soluble ionic form. The motivation would have been to prepare pharmaceutical products with optimal drug dosage and stability. Hence, a skilled artisan would have reasonable expectation of successfully producing an efficacious and stable drug.

Claims 20, 27, 33, and 39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gamache, et al. (WO 01/15677 A2; 03/2001), as applied to claims 19, 21-24, 26, 28-30, 32, 34-36, 38, 40-42, and 44-48 and further in view of Desai, et al. (5558876).

Gamache, et al. is as discussed above.

Gamache, et al. fails to teach quaternary ammonium salt

Desai et al. teaches a composition comprising 0.05% Bromfenac, 0.05% Disodium EDTA, and 0.01% Benzalkonium chloride.

It would have been obvious to one of ordinary skill in the art to incorporate benzalkonium chloride into the ophthalmic formulation. The motivation comes from the teaching that benzalkonium chloride acts as a preservative in ophthalmic

formulation. Hence, a skilled artisan would have had reasonable expectation of successfully producing similar efficacy and results.

Claims 25, 31, 37, and 43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gamache, et al. (WO 01/15677 A2; 03/2001), as applied to claims 19, 21-24, 26, 28-30, 32, 34-36, 38, 40-42, and 44-48 and further in view of Ogawa, et al. (US 4910225 A) and De Bruiju et al. (US 6162393 A).

Gamache, et al. is as discussed above.

Gamache, et al. fails to teach sodium tetraborate, sodium sulfite, and polyvinylpyrrolidone, boric acid.

Ogawa et al. teaches sodium sulfite and polyvinyl pyrrolidone increased the stability of an eye drop formulation remarkably. The pH adjustment is generally conducted with sodium hydroxide or hydrochloric acid, for instance, and it is advisable to form a buffer solution by combined use of, for example, sodium acetate, sodium borate or sodium phosphate and acetic acid, boric acid or phosphoric acid, respectively.

De Bruiju et al. various buffer systems such as citrate, phosphate (appropriate mixtures of Na.sub.2 HPO.sub.4, NaH.sub.2 PO.sub.4, and KH.sub.2 PO.sub.4), borate (boric acid, sodium tetraborate) potassium metaborate and mixtures), bicarbonate, and tromethamine and other appropriate nitrogen-containing buffers (such as ACES, BES, BICINE, BIS-Tris, BIS-Tris Propane, HEPES, HEPPS, imidazole, MES, MOPS, PIPES, TAPS, TES, Tricine) can be used to ensure a physiologic pH between about pH 6.5 and 8.5 in an eye solution.

It would have been obvious to one of ordinary skill in the art to incorporate sodium tetraborate, sodium sulfite, and polyvinylpyrrolidone, boric acid into the ophthalmic formulation. The motivation comes from the teaching that sodium sulfite and polyvinyl pyrrolidone increased the stability of an eye drop formulation and further that various buffer systems such as citrate, phosphate (appropriate mixtures of Na.sub.2 HPO.sub.4, NaH.sub.2 PO.sub.4, and KH.sub.2 PO.sub.4), borate (boric acid, sodium tetraborate) potassium metaborate and mixtures), bicarbonate, and tromethamine and other appropriate nitrogen-containing buffers (such as ACES, BES, BICINE, BIS-Tris, BIS-Tris Propane, HEPES, HEPPS, imidazole, MES, MOPS, PIPES, TAPS, TES, Tricine) can be used to ensure a physiologic pH between about pH 6.5 and 8.5 in an eye solution. Hence, a skilled artisan would have had reasonable expectation of successfully producing similar efficacy and results.

Double Patenting

Claims 19, 21-24, 26, 28-30, 32, 34-36, 38, 40-42, and 44-48 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-8 of U.S. Patent No. 7829544. Although the claims at issue are not identical, they are not patentably distinct from each other because the claims in the patent are drawn to an aqueous solution preparation comprising (a) an aminoglycoside antibiotic or its pharmacologically acceptable salt, (b) bromfenac or its pharmacologically acceptable salt and (c) nicotinamide whereas the claims herein are drawn to a stable aqueous liquid preparation comprising: (a) a first component; and (b) a second component; wherein the first component is 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a

pharmacologically acceptable salt thereof or a hydrate thereof, wherein the hydrate is at least one selected from a 1/2 hydrate, 1 hydrate, and 3/2 hydrate; the second component is tyloxapol and is present in said liquid preparation in an amount sufficient to stabilize said first component; and wherein said stable liquid preparation is formulated for ophthalmic administration.

Claims 19, 21-24, 26, 28-30, 32, 34-36, 38, 40-42, and 44-48 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-22 of U.S. Patent No. 8129431. Although the claims at issue are not identical, they are not patentably distinct from each other because the claims in the patent are drawn to an aqueous liquid preparation consisting essentially of the following two components, wherein the first component is 2-amino-3-(4-bromobenzoyl)phenylaceticacid or a pharmacologically acceptable salt thereof or a hydrate thereof, wherein the hydrate is at least one selected from a 1/2 hydrate, 1 hydrate, and 3/2 hydrate and the second component is tyloxapol wherein said liquid preparation is formulated for ophthalmic administration, and wherein when a quaternary ammonium compound is included in said liquid preparation, the quaternary ammonium compound is benzalkonium chloride whereas the claims herein are drawn to a stable aqueous liquid preparation comprising: (a) a first component; and (b) a second component; wherein the first component is 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof, wherein the hydrate is at least one selected from a 1/2 hydrate, 1 hydrate, and 3/2 hydrate; the second component is tyloxapol and is present

in said liquid preparation in an amount sufficient to stabilize said first component; and wherein said stable liquid preparation is formulated for ophthalmic administration.

Claims 19, 21-24, 26, 28-30, 32, 34-36, 38, 40-42, and 44-48 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-5 of copending Application No. 11755662. Although the claims at issue are not identical, they are not patentably distinct from each other because the claims in the copending application are 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 a stable aqueous liquid preparation comprising: (a) a first component; and (b) a second component; wherein the first component is 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof, wherein the hydrate is at least one selected from a 1/2 hydrate, 1 hydrate, and 3/2 hydrate; the second component is tyloxapol and is present in said liquid preparation in an amount sufficient to stabilize said first component; and wherein said stable liquid preparation is formulated for ophthalmic administration.

This is a provisional nonstatutory double patenting rejection.

Claims 19, 21-24, 26, 28-30, 32, 34-36, 38, 40-42, and 44-48 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-5 of copending Application No. 13353653. Although the claims at issue are not identical, they are not patentably distinct from each other because the claims in the copending application are drawn to 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 polyoxyl 40 stearate is selected from a range of a minimum concentration of 0.02 w/v % to a maximum concentration of O. 1 w/v% whereas the claims herein are drawn to a stable aqueous liquid preparation comprising: (a) a first component; and (b) a second component; wherein the first component is 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof, wherein the hydrate is at least one selected from a 1/2 hydrate, 1 hydrate, and 3/2 hydrate; the second component is tyloxapol and is present in said liquid preparation in an amount sufficient to stabilize said first component; and wherein said stable liquid preparation is formulated for ophthalmic administration.

This is a provisional nonstatutory double patenting rejection.

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

Notice of References Cited	Application/Control No. 13/687,242	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-5,558,876	09-1996	Desai et al.	424/427
*	B	US-4,910,225	03-1990	Ogawa et al.	514/561
*	C	US-6,162,393	12-2000	De Bruiju et al.	422/28
	D	US-			
	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	WO 0115677 A2	03-2001	World Intellect	GAMACHE D A et al.	
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

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

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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.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Named Inventor	:	
Shirou SAWA	:	
Serial No. NEW	:	
Filed November 28, 2012	:	
AQUEOUS LIQUID PREPARATION CONTAINING 2-AMINO-3-(4-BROMOBENZOYL)PHENYLACETIC ACID **(Rule 1.53(b) Divisional of Serial No. 13/353,653, Filed January 19, 2012)**	:	Attorney Docket No. 2012_5420

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, Applicant requests 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 applications (Serial No. 13/353,653, 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,

/Warren M. Cheek/

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November 28, 2012

Sheet 1 of 3

INFORMATION DISCLOSURE STATEMENT

FORM PTO/SB/08 A&B (*modified*) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE LIST OF REFERENCES CITED BY APPLICANT(S) (*Use several sheets if necessary*) Date Submitted to PTO: November 28, 2012	**ATTY DOCKET NO.** 2012_5420	**SERIAL NO.** NEW
	FIRST NAMED INVENTOR Shirou SAWA	
	FILING DATE November 28, 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
/L.S./	BA	9-503791	4/1997	JP				
	BB	2-124819	5/1990	JP				
	BC	1-104023	4/1989	JP				
	BD	00/59475	10/2000	WO				
	BE	11-228404	8/1999	JP			Yes	
	BF	5-223052	8/1993	JP			Abstract	
	BG	62-126124	6/1987	JP				No

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 3

INFORMATION DISCLOSURE STATEMENT

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

U.S. DEPARTMENT OF COMMERCE
PATENT AND TRADEMARK OFFICE

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

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2012_5420	NEW
FIRST NAMED INVENTOR	
Shirou SAWA	
FILING DATE	**GROUP**
November 28, 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
/L.S./	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	DATE CONSIDERED

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U.S. DEPARTMENT OF COMMERCE
PATENT AND TRADEMARK OFFICE

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FIRST NAMED INVENTOR	
Shirou SAWA	
FILING DATE	**GROUP**
November 28, 2012	

U.S. PATENT DOCUMENTS

*EXAMINER INITIAL		DOCUMENT NUMBER	DATE	NAME	CLASS	SUBCLASS	FILING DATE IF APPROPRIATE
/L.S./	AP	6,383,471	5/2002	Chen et al.			
/L.S./	AQ	5,942,508	8/1999	Sawa			
/L.S./	AR	6,274,592	8/2001	Sawa			
/L.S./	AS	2001/0056098	12/2001	Sawa			
	AT						
	AU						
	AV						
	AW						

FOREIGN PATENT DOCUMENTS

		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION YES	TRANSLATION NO
/L.S./	BN	02083323	3/1990	JP				
/L.S./	BO	2002-308764	10/2002	JP				
	BP							
	BQ							
	BR							

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

	CE	
	CF	
	CG	
	CH	

EXAMINER	/Layla Soroush/	DATE CONSIDERED	

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

Search Notes	Application/Control No.	Applicant(s)/Patent under Reexamination	
	13/687,242	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
bromfenac and tyloxapol	7/12/2013	LS
SAWA, SHIROU FUJITA, SHUHEI	7/12/2013	LS

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United States Patent and Trademark Office
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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
13/687,242	11/28/2012	Shirou SAWA	2012_5420

CONFIRMATION NO. 1577

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

PUBLICATION NOTICE

OC000000060429573

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

Publication No.US-2013-0090384-A1
Publication Date:04/11/2013

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

First Named Inventor	:	Attorney Docket No. 2012_5420
Shirou SAWA	:	**Confirmation No. 1577**
Serial No. 13/687,242	:	Group Art Unit 1627
Filed November 28, 2012	:	Examiner Layla Soroush
AQUEOUS LIQUID PREPARATION CONTAINING 2-AMINO-3-(4-BROMOBENZOYL)PHENYLACETIC ACID	:	**Mail Stop: AMENDMENT**

RESPONSE TO ELECTION OF SPECIES REQUIREMENT

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

Sir/Madam:

Pursuant to the requirement set forth in the Office Action mailed March 25, 2013, Applicant hereby elects benzalkonium chloride as the species of quarternary ammonium salts. Claims 19-48 read on the elected species.

In view of this election, a full examination on the merits of the present application is respectfully requested.

Respectfully submitted,

/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: 2013.04.09 13:56:33 -04'00'

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

WMC/dlk
Washington, D.C. 20005-1503
Telephone (202) 721-8200
Facsimile (202) 721-8250
April 9, 2013

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:	15470120
Application Number:	13687242
International Application Number:	
Confirmation Number:	1577
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_5420
Receipt Date:	09-APR-2013
Filing Date:	28-NOV-2012
Time Stamp:	15:26:10
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_Response.pdf	173201 e9d8b05dd0402df742283e607655996a60d06179	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):	173201

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 (09-11)
Approved for use through 1/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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.

PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 13/687,242	Filing Date 11/28/2012	☐ 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 **04/09/2013**

	(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))	* 30	Minus	** 30	= 0	X $80 =	0
Independent (37 CFR 1.16(h))	* 3	Minus	***3	= 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
/LINDA BADIE/

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/687,242	11/28/2012	INV001Shirou SAWA	2012_5420	1577

513 7590 03/25/2013

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
03/25/2013	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.	Applicant(s)	
	13/687,242	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 *15 January 2013*.

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) *19-48* 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) *19-48* 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).

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) ☐ 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

Election/Restrictions

1. 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 quaternary ammonium salts.

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).

2. 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 quaternary ammonium salts are represented by the different species or possible other choices, each of which consist of different chemical and physical properties.

3. 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.

4. 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).

/Layla Soroush/

Examiner, Art Unit 1627

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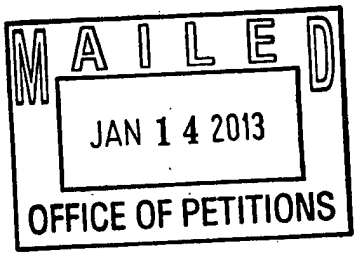
Washington DC 20005-1503



Doc Code: TRACK1.GRANT

Decision Granting Request for Prioritized Examination (Track I or After RCE)	Application No.: 13/687,242

1. THE REQUEST FILED November 28, 2012 IS **GRANTED.**

The above-identified application has met the requirements for prioritized examination

A. ☒ for an original nonprovisional application (Track I).
B. ☐ for an application undergoing continued examination (RCE).

2. **The above-identified application will undergo prioritized examination.** The application will be accorded special status throughout its entire course of prosecution until one of the following occurs:

A. filing a **petition for extension of time** to extend the time period for filing a reply;

B. filing an **amendment to amend the application to contain more than four independent claims, more than thirty total claims**, or a multiple dependent claim;

C. filing a **request for continued examination**;

D. filing a notice of appeal;

E. filing a request for suspension of action;

F. mailing of a notice of allowance;

G. mailing of a final Office action;

H. completion of examination as defined in 37 CFR 41.102; or

I. abandonment of the application.

Telephone inquiries with regard to this decision should be directed to Brian W. Brown at 571-272-5338.

/Brian W. Brown/
[*Signature*]

Petitions Examiner, Office of Petitions
(Title)

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

２０１３年　１月　４日

特許庁長官
Commissioner,
Japan Patent Office　深野弘行

【書類名】特許願

【整理番号】598-03

【提出日】平成15年 1月21日

【あて先】特許庁長官　殿

【国際特許分類】

A61K　9/08

A61K 31/195

A61K 47/18

A61K 47/32

A61P 27/02

A61P 27/16

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【特許出願人】

【識別番号】000199175

【氏名又は名称】千寿製薬株式会社

【代理人】

【識別番号】100118360

【弁理士】

【氏名又は名称】松田　玲子

【電話番号】06-6201-9627

【手数料の表示】

【予納台帳番号】004167

【納付金額】21,000

【提出物件の目録】

【物件名】明細書　1

【物件名】要約書　1

【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。

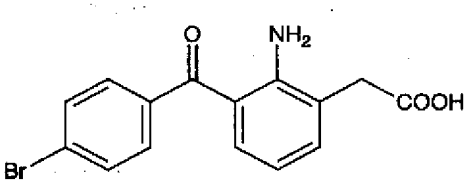
【０００２】

【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。

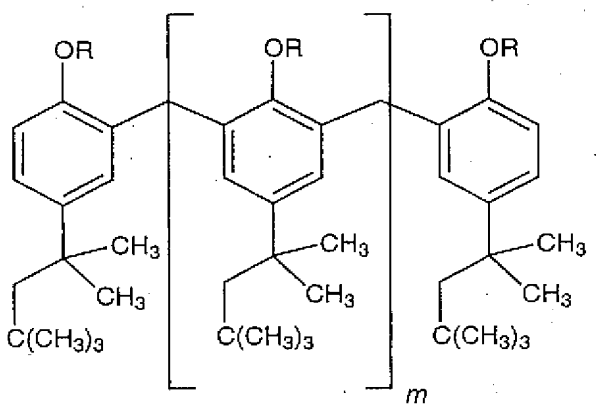
【００１５】

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

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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

SUPPLEMENTAL **Application Data Sheet 37 CFR 1.76**	Attorney Docket Number	2012_5420
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Title of Invention	AQUEOUS LIQUID PREPARATION CONTAINING 2-AMINO-3-(4-BROMOBENZOYL)PHENYLACETIC ACID	

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Postal Code	~~675-0054~~ 651-2241	**Country**	JP

All Inventors Must Be Listed - Additional Inventor Information blocks may be generated within this form by selecting the **Add** button. Add

Correspondence Information:

SUPPLEMENTAL **Application Data Sheet 37 CFR 1.76**	Attorney Docket Number	2012_5420
	Application Number	13/687,242
Title of Invention	AQUEOUS LIQUID PREPARATION CONTAINING 2-AMINO-3-(4-BROMOBENZOYL)PHENYLACETIC ACID	

Enter either Customer Number or complete the Correspondence Information section below.
For further information see 37 CFR 1.33(a).

☐ **An Address is being provided for the correspondence Information of this application.**

Customer Number	00513		
Email Address	wip@wenderoth.com	Add Email	Remove Email

Application Information:

Title of the Invention	AQUEOUS LIQUID PREPARATION CONTAINING 2-AMINO-3-(4-BROMOBENZOYL) PHENYLACETIC ACID		
Attorney Docket Number	2012_5420	**Small Entity Status Claimed**	☐
Application Type	Nonprovisional		
Subject Matter	Utility		
Suggested Class (if any)		**Sub Class (if any)**	
Suggested Technology Center (if any)			
Total Number of Drawing Sheets (if any)		**Suggested Figure for Publication (if any)**	

Publication Information:

☐ Request Early Publication (Fee required at time of Request 37 CFR 1.219)

☐ **Request Not to Publish.** I hereby request that the attached application not be published under 35 U.S.C. 122(b) and certify that the invention disclosed in the attached application **has not and will not** be the subject of an application filed in another country, or under a multilateral international agreement, that requires publication at eighteen months after filing.

Representative Information:

Representative information should be provided for all practitioners having a power of attorney in the application. Providing this information in the Application Data Sheet does not constitute a power of attorney in the application (see 37 CFR 1.32).
Either enter Customer Number or complete the Representative Name section below. If both sections are completed the customer Number will be used for the Representative Information during processing.

Please Select One:	◉ Customer Number	○ US Patent Practitioner	○ Limited Recognition (37 CFR 11.9)
Customer Number	00513		

Domestic Benefit/National Stage Information:

This section allows for the applicant to either claim benefit under 35 U.S.C. 119(e), 120, 121, or 365(c) or indicate National Stage entry from a PCT application. Providing this information in the application data sheet constitutes the specific reference required by 35 U.S.C. 119(e) or 120, and 37 CFR 1.78.

Prior Application Status	Pending	Remove

SUPPLEMENTAL **Application Data Sheet 37 CFR 1.76**	Attorney Docket Number	2012_5420
	Application Number	13/687,242
Title of Invention	AQUEOUS LIQUID PREPARATION CONTAINING 2-AMINO-3-(4-BROMOBENZOYL)PHENYLACETIC ACID	

Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
	Division of	13/353653	2012-01-19
Prior Application Status	Patented	Remove	

Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
13/353653	Division of	10/525006	2005-03-28	8129431	2012-03-06

Prior Application Status	Expired	Remove	
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
10/525006	a 371 of international	PCT/JP2004/000350	2004-01-16

Additional Domestic Benefit/National Stage Data may be generated within this form by selecting the **Add** button.

Foreign Priority Information:

This section allows for the applicant to claim benefit of foreign priority and to identify any prior foreign application for which priority is not claimed. Providing this information in the application data sheet constitutes the claim for priority as required by 35 U.S.C. 119(b) and 37 CFR 1.55(a).

Remove

Application Number	Country[i]	Filing Date (YYYY-MM-DD)	Priority Claimed
2003-012427	JP	2003-01-21	(•) Yes ( ) No

Additional Foreign Priority Data may be generated within this form by selecting the **Add** button.

Authorization to Permit Access:

☒ Authorization to Permit Access to the Instant Application by the Participating Offices

If checked, the undersigned hereby grants the USPTO authority to provide the European Patent Office (EPO), the Japan Patent Office (JPO), the Korean Intellectual Property Office (KIPO), the World Intellectual Property Office (WIPO), and any other intellectual property offices in which a foreign application claiming priority to the instant patent application is filed access to the instant patent application. See 37 CFR 1.14(c) and (h). This box should not be checked if the applicant does not wish the EPO, JPO, KIPO, WIPO, or other intellectual property office in which a foreign application claiming priority to the instant patent application is filed to have access to the instant patent application.

In accordance with 37 CFR 1.14(h)(3), access will be provided to a copy of the instant patent application with respect to: 1) the instant patent application-as-filed; 2) any foreign application to which the instant patent application claims priority under 35 U.S.C. 119(a)-(d) if a copy of the foreign application that satisfies the certified copy requirement of 37 CFR 1.55 has been filed in the instant patent application; and 3) any U.S. application-as-filed from which benefit is sought in the instant patent application.

In accordance with 37 CFR 1.14(c), access may be provided to information concerning the date of filing this Authorization.

SUPPLEMENTAL **Application Data Sheet 37 CFR 1.76**	Attorney Docket Number	2012_5420
	Application Number	13/687,242
Title of Invention	AQUEOUS LIQUID PREPARATION CONTAINING 2-AMINO-3-(4-BROMOBENZOYL)PHENYLACETIC ACID	

Applicant Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

Applicant 1

If the applicant is the inventor (or the remaining joint inventor or inventors under 37 CFR 1.45), this section should not be completed. The information to be provided in this section is the name and address of the legal representative who is the applicant under 37 CFR 1.43; or the name and address of the assignee, person to whom the inventor is under an obligation to assign the invention, or person who otherwise shows sufficient proprietary interest in the matter who is the applicant under 37 CFR 1.46. If the applicant is an applicant under 37 CFR 1.46 (assignee, person to whom the inventor is obligated to assign, or person who otherwise shows sufficient proprietary interest) together with one or more joint inventors, then the joint inventor or inventors who are also the applicant should be identified in this section.

◉ Assignee	○ Legal Representative under 35 U.S.C. 117
○ Person to whom the inventor is obligated to assign.	○ Person who shows sufficient proprietary interest

If applicant is the legal representative, indicate the authority to file the patent application, the inventor is:

Name of the Deceased or Legally Incapacitated Inventor :

If the Assignee is an Organization check here. ☒

Organization Name	SENJU PHARMACEUTICAL CO., LTD.		
Mailing Address Information:			
Address 1	5-8, Hiranomachi 2-chome, Chuo-ku, Osaka-shi,		
Address 2			
City	Osaka	**State/Province**	
Country JP		Postal Code	541-0046
Phone Number		Fax Number	
Email Address			

Additional Applicant Data may be generated within this form by selecting the Add button.

Signature:

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

Signature	/Warren M. Cheek/ Digitally signed by /Warren M. Cheek/ DN: cn=/Warren M. Cheek/, o, ou, email=wcheek@wenderoth.com, c=US Date: 2013.01.04 11:15:32 -05'00'			Date (YYYY-MM-DD)	2013-01-04
First Name	Warren	Last Name	Cheek	Registration Number	33367

Additional Signature may be generated within this form by selecting the Add button.

SUPPLEMENTAL **Application Data Sheet 37 CFR 1.76**	Attorney Docket Number	2012_5420
	Application Number	13/687,242
Title of Invention	AQUEOUS LIQUID PREPARATION CONTAINING 2-AMINO-3-(4-BROMOBENZOYL)PHENYLACETIC ACID	

This collection of information is required by 37 CFR 1.76. 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 23 minutes to complete, including gathering, preparing, and submitting the completed application data sheet 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, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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 the Freedom of Information Act requires disclosure of these records.

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 inspections 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.

Electronic Acknowledgement Receipt

EFS ID:	14616894
Application Number:	13687242
International Application Number:	
Confirmation Number:	1577
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_5420
Receipt Date:	04-JAN-2013
Filing Date:	28-NOV-2012
Time Stamp:	14:50:44
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	Application Data Sheet	AttachA_ADS.pdf	1346295 7c858ca2158a893766ef21f9268eda04570d3183	no	6

Warnings:	
Information:	

This is not an USPTO supplied ADS fillable form	
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.	
Total Files Size (in bytes):	1346295

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.

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number: 13/687,242

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	390
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))	30 minus 20 =	* 10			OR	x 62 =	620
INDEPENDENT CLAIMS (37 CFR 1.16(h))	3 minus 3 =	*				x 250 =	0.00
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	1880

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.

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
13/687,242	11/28/2012	Shirou SAWA	2012_5420

CONFIRMATION NO. 1577

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

POA ACCEPTANCE LETTER

OC000000058318646

Date Mailed: 01/03/2013

NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 11/28/2012.

The Power of Attorney in this application is accepted. Correspondence in this application will be mailed to the above address as provided by 37 CFR 1.33.

/yhailu/

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

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	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
13/687,242	11/28/2012	1629	2180	2012_5420	30	3

CONFIRMATION NO. 1577

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

FILING RECEIPT

OC000000058318973

Date Mailed: 01/03/2013

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**

Inventor(s)

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

Applicant(s)

SENJU PHARMACEUTICAL CO., LTD., Osaka, JAPAN

Assignment For Published Patent Application

SENJU PHARMACEUTICAL CO., LTD., Osaka, JAPAN

Power of Attorney: The patent practitioners associated with Customer Number 00513

Domestic Priority data as claimed by applicant

This application is a DIV of 13/353,653 01/19/2012
which is a DIV of 10/525,006 03/28/2005 PAT 8129431
which is a 371 of PCT/JP2004/000350 01/16/2004

Foreign Applications (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

Permission to Access - A proper **Authorization to Permit Access to Application by Participating Offices** (PTO/SB/39 or its equivalent) has been received by the USPTO.

Request to Retrieve - This application either claims priority to one or more applications filed in an intellectual property Office that participates in the Priority Document Exchange (PDX) program or contains a proper **Request to**

Retrieve Electronic Priority Application(s) (PTO/SB/38 or its equivalent). Consequently, the USPTO will attempt to electronically retrieve these priority documents.

If Required, Foreign Filing License Granted: 12/21/2012

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 13/687,242**

Projected Publication Date: 04/11/2013

Non-Publication Request: No

Early Publication Request: No

Title

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

Preliminary Class

514

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at http://www.uspto.gov/web/offices/pac/doc/general/index.html.

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4158).

LICENSE FOR FOREIGN FILING UNDER

Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

GRANTED

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This license is to be retained by the licensee and may be used at any time on or after the effective date thereof unless it is revoked. This license is automatically transferred to any related applications(s) filed under 37 CFR 1.53(d). This license is not retroactive.

The grant of a license does not in any way lessen the responsibility of a licensee for the security of the subject matter as imposed by any Government contract or the provisions of existing laws relating to espionage and the national security or the export of technical data. Licensees should apprise themselves of current regulations especially with respect to certain countries, of other agencies, particularly the Office of Defense Trade Controls, Department of State (with respect to Arms, Munitions and Implements of War (22 CFR 121-128)); the Bureau of Industry and Security, Department of Commerce (15 CFR parts 730-774); the Office of Foreign AssetsControl, Department of Treasury (31 CFR Parts 500+) and the Department of Energy.

NOT GRANTED

No license under 35 U.S.C. 184 has been granted at this time, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" DOES NOT appear on this form. Applicant may still petition for a license under 37 CFR 5.12, if a license is desired before the expiration of 6 months from the filing date of the application. If 6 months has lapsed from the filing date of this application and the licensee has not received any indication of a secrecy order under 35 U.S.C. 181, the licensee may foreign file the application pursuant to 37 CFR 5.15(b).

UTILITY
PATENT APPLICATION
TRANSMITTAL
(Only for new nonprovisional applications under 37 CFR 1.53(b)

Attorney Docket No.: 2012_5420

First Named Inventor: Shirou SAWA

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. [] Small Entity Status is hereby asserted.

2. [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))

3. [] Drawing(s) *(35 USC 113)* *[Total Sheets:]*

4. [] Declaration(s) *[Total Pages:]*
a. [] Copy from a prior application (37 CFR 1.63(d)(1))
(for continuation/divisional with (37 CFR 1.63(d)(1)) completed)

5. [X] Application Data Sheet (see 37 CFR 1.76)

6. [] CD-ROM or CD-R in duplicate, large table or computer program *(Appendix)*

7. [] 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

8. [] Power of Attorney

9. [X] Information Disclosure Statement (IDS)/PTO/SB/08
[] Copies of IDS Citations

10. [X] Preliminary Amendment

11. [] 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.

12. [X] Other - 2 Executed Declarations; Request for Prioritized Examination

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. 13/353,653

Prior Application Information: Examiner: Layla Soroush Group Art Unit: 1627

19. CORRESPONDENCE ADDRESS

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November 28, 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.

PTO/AIA/14 (08-12)
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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	2012_5420
	Application Number	
Title of Invention	AQUEOUS LIQUID PREPARATION CONTAINING 2-AMINO-3-(4-BROMOBENZOYL)PHENYLACETIC ACID	

The application data sheet is part of the provisional or nonprovisional application for which it is being submitted. The following form contains the bibliographic data arranged in a format specified by the United States Patent and Trademark Office as outlined in 37 CFR 1.76.
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☐ Portions or all of the application associated with this Application Data Sheet may fall under a Secrecy Order pursuant to 37 CFR 5.2 (Paper filers only. Applications that fall under Secrecy Order may not be filed electronically.)

Inventor Information:

Inventor 1 Remove

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All Inventors Must Be Listed - Additional Inventor Information blocks may be generated within this form by selecting the **Add** button. Add

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	2012_5420
	Application Number	
Title of Invention	AQUEOUS LIQUID PREPARATION CONTAINING 2-AMINO-3-(4-BROMOBENZOYL)PHENYLACETIC ACID	

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Customer Number	00513		
Email Address	wlp@wenderoth.com	Add Email	Remove Email

Application Information:

Title of the Invention	AQUEOUS LIQUID PREPARATION CONTAINING 2-AMINO-3-(4-BROMOBENZOYL) PHENYLACETIC ACID		
Attorney Docket Number	2012_5420	**Small Entity Status Claimed**	☐
Application Type	Nonprovisional		
Subject Matter	Utility		
Suggested Class (if any)		**Sub Class (if any)**	
Suggested Technology Center (if any)			
Total Number of Drawing Sheets (if any)		**Suggested Figure for Publication (if any)**	

Publication Information:

☐ Request Early Publication (Fee required at time of Request 37 CFR 1.219)

☐ **Request Not to Publish.** I hereby request that the attached application not be published under 35 U.S.C. 122(b) and certify that the invention disclosed in the attached application **has not and will not** be the subject of an application filed in another country, or under a multilateral international agreement, that requires publication at eighteen months after filing.

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Customer Number	00513		

Domestic Benefit/National Stage Information:

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Prior Application Status	Pending	Remove

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	2012_5420
	Application Number	
Title of Invention	AQUEOUS LIQUID PREPARATION CONTAINING 2-AMINO-3-(4-BROMOBENZOYL)PHENYLACETIC ACID	

Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
	Division of	13/353653	2012-01-19
Prior Application Status	Patented		Remove

Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
13/353653	Division of	10/525006	2005-03-28	8129431	2012-03-06

Prior Application Status	Expired		Remove

Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
10/525006	a 371 of international	PCT/JP2004/000350	2004-01-16

Additional Domestic Benefit/National Stage Data may be generated within this form by selecting the **Add** button. Add

Foreign Priority Information:

This section allows for the applicant to claim benefit of foreign priority and to identify any prior foreign application for which priority is not claimed. Providing this information in the application data sheet constitutes the claim for priority as required by 35 U.S.C. 119(b) and 37 CFR 1.55(a).

Remove

Application Number	Country i	Filing Date (YYYY-MM-DD)	Priority Claimed
2003-012427	JP	2003-01-21	◉ Yes ○ No

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Authorization to Permit Access:

☒ Authorization to Permit Access to the Instant Application by the Participating Offices

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In accordance with 37 CFR 1.14(h)(3), access will be provided to a copy of the instant patent application with respect to: 1) the instant patent application-as-filed; 2) any foreign application to which the instant patent application claims priority under 35 U.S.C. 119(a)-(d) if a copy of the foreign application that satisfies the certified copy requirement of 37 CFR 1.55 has been filed in the instant patent application; and 3) any U.S. application-as-filed from which benefit is sought in the instant patent application.

In accordance with 37 CFR 1.14(c), access may be provided to information concerning the date of filing this Authorization.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	2012_5420
	Application Number	
Title of Invention	AQUEOUS LIQUID PREPARATION CONTAINING 2-AMINO-3-(4-BROMOBENZOYL)PHENYLACETIC ACID	

Applicant Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

Applicant 1

If the applicant is the inventor (or the remaining joint inventor or inventors under 37 CFR 1.45), this section should not be completed. The information to be provided in this section is the name and address of the legal representative who is the applicant under 37 CFR 1.43; or the name and address of the assignee, person to whom the inventor is under an obligation to assign the invention, or person who otherwise shows sufficient proprietary interest in the matter who is the applicant under 37 CFR 1.46. If the applicant is an applicant under 37 CFR 1.46 (assignee, person to whom the inventor is obligated to assign, or person who otherwise shows sufficient proprietary interest) together with one or more joint inventors, then the joint inventor or inventors who are also the applicant should be identified in this section.

Remove

◉ Assignee	○ Legal Representative under 35 U.S.C. 117
○ Person to whom the inventor is obligated to assign.	○ Person who shows sufficient proprietary interest

If applicant is the legal representative, indicate the authority to file the patent application, the inventor is:

Name of the Deceased or Legally Incapacitated Inventor :

If the Assignee is an Organization check here. ☒

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City	Osaka	**State/Province**	
Country [i]	JP	Postal Code	541-0046
Phone Number		Fax Number	
Email Address			

Additional Applicant Data may be generated within this form by selecting the Add button. Add

Signature:

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

Signature	/warren cheek/			Date (YYYY-MM-DD)	2012-11-28
First Name	Warren	Last Name	Cheek	Registration Number	33367

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	2012_5420
	Application Number	
Title of Invention	AQUEOUS LIQUID PREPARATION CONTAINING 2-AMINO-3-(4-BROMOBENZOYL)PHENYLACETIC ACID	

This collection of information is required by 37 CFR 1.76. 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 23 minutes to complete, including gathering, preparing, and submitting the completed application data sheet 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, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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DESCRIPTION

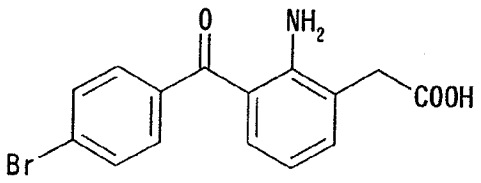
AQUEOUS LIQUID PREPARATION CONTAINING 2-AMINO-3-(4-BROMOBENZOYL)PHENYLACETIC ACID

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.

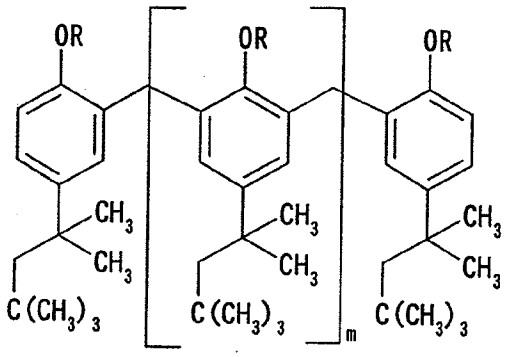
In the aqueous liquid preparation of the present invention, the content (concentration range) of 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof is usually about 0.01 to 0.5 w/v %, preferably about 0.05 to 0.2 w/v %, especially about 0.1 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 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	2.1×10^{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 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	2.1×10^{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 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 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.).

TRANSMITTAL FOR POWER OF ATTORNEY TO ONE OR MORE REGISTERED PRACTITIONERS

NOTE: This form is to be submitted with the Power of Attorney by Applicant form (PTO/AIA/82B or equivalent) to identify the application to which the Power of Attorney is directed, in accordance with 37 CFR 1.5. If the Power of Attorney by Applicant form is not accompanied by this transmittal form or an equivalent, the Power of Attorney will not be recognized in the application.

Application Number	NEW
Filing Date	November 28, 2012
First Named Inventor	Shirou SAWA
Title	AQUEOUS LIQUID PREPARATION CONTAINING 2-AMINO-3-(4-BROMOBENZOYL)PHENYLACETIC ACID
Art Unit	
Examiner Name	
Attorney Docket Number	2012_5420
Applicant's or Agent's Reference No.	DIV of S30F1252(US)DIV

SIGNATURE of Applicant or Patent Practitioner

Signature	/Warren M. Cheek/ Digitally signed by /Warren M. Cheek/ DN: cn=/Warren M. Cheek/, o, ou, email=wcheek@wenderoth.com, c=US Date: 2012.11.28 12:01:21 -05'00'	Date	**November 28, 2012**
Name	Warren M. Cheek	Telephone	(202) 721-8200
Registration Number	33,367		

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

Total of 1 forms are submitted.

GENERAL POWER OF ATTORNEY BY APPLICANT FOR UNITED STATES PATENT

I hereby revoke all previous powers of attorney given in the application referenced in the attached transmittal letter (form PTO/AIA/82A or equivalent).

I hereby appoint the practitioners associated with the following Customer Number for **Wenderoth, Lind & Ponack, L.L.P.:**

00513

as my/our attorneys or agents, and to transact all business in the United States Patent and Trademark Office in connection with the application referenced in the attached transmittal letter (form PTO/AIA/82A or equivalent).

Please recognize or change the **correspondence address** for the application referenced in the attached transmittal letter to the address associated with the above-mentioned **Customer Number**

I am the Applicant:

- [ ] Inventor or Joint Inventor
- [ ] Legal Representative of a Deceased or Legally Incapacitated Inventor
- [X] Assignee or Person to Whom the Inventor is Under an Obligation to Assign
- [ ] Person Who Otherwise Shows Sufficient Proprietary Interest (e.g., a petition under 37 CFR 1.46(b)(2) was granted in the application or is currently being filed in this document)

SIGNATURE of Applicant for Patent

Signature		Date	2012, 11, 19
Name	Shuhei YOSHIDA		
Title	Executive Vice President		
Company	SENJU PHARMACEUTICAL CO., LTD.		

Note: Signature - this form must be signed by the Applicant or a person authorized to act on behalf of Applicant.

Submit multiple forms for more than one signature
Total of 1 forms are submitted.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Named Inventor	:	
Shirou SAWA	:	
Serial No. NEW	:	
Filed November 28, 2012	:	
AQUEOUS LIQUID PREPARATION CONTAINING 2-AMINO-3-(4-BROMOBENZOYL)PHENYLACETIC ACID **(Rule 1.53(b) Divisional of Serial No. 13/353,653, Filed January 19, 2012)**	:	Attorney Docket No. 2012_5420

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, Applicant requests 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 applications (Serial No. 13/353,653, 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,

/Warren M. Cheek/

Digitally signed by /Warren M. Cheek/
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Date: 2012.11.28 12:01:46 -05'00'

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November 28, 2012

Sheet 1 of 3

INFORMATION DISCLOSURE STATEMENT

FORM PTO/SB/08 A&B (*modified*) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE LIST OF REFERENCES CITED BY APPLICANT(S) (*Use several sheets if necessary*) Date Submitted to PTO: November 28, 2012	**ATTY DOCKET NO.** 2012_5420	**SERIAL NO.** NEW
	FIRST NAMED INVENTOR Shirou SAWA	
	FILING DATE November 28, 2012	**GROUP**

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 3	INFORMATION DISCLOSURE STATEMENT	
FORM PTO/SB/08 A&B (*modified*) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE LIST OF REFERENCES CITED BY APPLICANT(S) (*Use several sheets if necessary*) Date Submitted to PTO: November 28, 2012	**ATTY DOCKET NO.** 2012_5420	**SERIAL NO.** NEW
	FIRST NAMED INVENTOR Shirou SAWA	
	FILING DATE November 28, 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

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Sheet 3 of 3

INFORMATION DISCLOSURE STATEMENT

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

U.S. DEPARTMENT OF COMMERCE
PATENT AND TRADEMARK OFFICE

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

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2012_5420	NEW
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Shirou SAWA	
FILING DATE	**GROUP**
November 28, 2012	

U.S. PATENT DOCUMENTS

*EXAMINER INITIAL		DOCUMENT NUMBER	DATE	NAME	CLASS	SUBCLASS	FILING DATE IF APPROPRIATE
	AP	6,383,471	5/2002	Chen et al.			
	AQ	5,942,508	8/1999	Sawa			
	AR	6,274,592	8/2001	Sawa			
	AS	2001/0056098	12/2001	Sawa			
	AT						
	AU						
	AV						
	AW						

FOREIGN PATENT DOCUMENTS

		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION YES	TRANSLATION NO
	BN	02083323	3/1990	JP				
	BO	2002-308764	10/2002	JP				
	BP							
	BQ							
	BR							

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

	CE	
	CF	
	CG	
	CH	

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	:	Attorney Docket No. 2012_5420
Shirou SAWA et al.	:	Confirmation No. NEW
Serial No. NEW	:	[Group Art Unit 1627]
Filed November 28, 2012	:	[Examiner Layla Soroush]
AQUEOUS LIQUID PREPARATION CONTAINING 2-AMINO-3-(4-BROMOBENZOYL)PHENYLACETIC ACID **(Rule 1.53(b) Divisional of Serial No. 13/353,653 Filed January 19, 2012)**	:	**Mail Stop: AMENDMENT**

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.

AMENDMENTS TO THE SPECIFICATION

Page 1, immediately after the title, please insert the paragraph as follows:

This is a divisional of Serial No. 13/353,653 filed January 19, 2012, which is a divisional of Serial No. 10/525,006, filed March 28, 2005, now issued as U.S. Patent No. 8,129,431, which is a U.S. national stage of International Application No. PCT/JP2004/000350 filed January 16, 2004.

AMENDMENTS TO THE CLAIMS

1-18. (Canceled)

19. (New) A stable aqueous liquid preparation comprising: (a) a first component; and (b) a second component; wherein the first component is 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof, wherein the hydrate is at least one selected from a 1/2 hydrate, 1 hydrate, and 3/2 hydrate; the second component is tyloxapol and is present in said liquid preparation in an amount sufficient to stabilize said first component; and wherein said stable liquid preparation is formulated for ophthalmic administration.

20. (New) The aqueous liquid preparation according to claim 19, further comprising a quaternary ammonium salt.

21. (New) The aqueous liquid preparation according to claim 19, wherein the first component is a 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt.

22. (New) The aqueous liquid preparation according to claim 19, wherein the concentration of tyloxapol is from about 0.01 w/v % to about 0.05 w/v %; and wherein the first component is a 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt, wherein the concentration of the 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt is from about 0.01 to about 0.2 w/v %.

23. (New) The aqueous liquid preparation according to claim 22, wherein the concentration of the 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt is about 0.1 w/v %.

24. (New) The aqueous liquid preparation according to claim 19, wherein the pH is from about 7.5 to about 8.5.

25. (New) The stable aqueous liquid preparation of claim 19, wherein the stable aqueous liquid preparation consists essentially of: (a) 2-amino-3-(4- bromobenzoyl)phenylacetic acid sodium salt, (d) sodium tetraborate, (e) EDTA sodium salt, (f) benzalkonium chloride, (g) polyvinylpyrrolidone, and (h) sodium sulfite, wherein said liquid preparation is formulated for ophthalmic administration, and wherein the concentration of the 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt is from about 0.02 w/v% to about 0.1 w/v %.

26. (New) A stable aqueous liquid preparation comprising: (a) a first component; and (b) a second component; wherein the first component is 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof, wherein the hydrate is at least one selected from a 1/2 hydrate, 1 hydrate, and 3/2 hydrate; the second component is tyloxapol; wherein said stable liquid preparation is formulated for ophthalmic administration; and wherein the stable aqueous liquid preparation is characterized in that greater than about 90% of the original amount of the first component remains in the preparation after storage at about 60 °C for 4 weeks.

27. (New) The aqueous liquid preparation according to claim 26, further comprising a quaternary ammonium salt.

28. (New) The stable aqueous liquid preparation of claim 26, wherein the stable aqueous liquid preparation is characterized in that greater than about 92% of the original amount of the first component remains in the preparation after storage at about 60 °C for 4 weeks.

29. (New) The aqueous liquid preparation according to claim 26, wherein the concentration of tyloxapol is from about 0.01 w/v % to about 0.05 w/v %; and wherein the first component is a 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt, wherein the concentration of the 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt is from about 0.01 to about 0.2 w/v %.

30. (New) The aqueous liquid preparation according to claim 29, wherein the pH is from about 7.5 to about 8.5.

31. (New) The stable aqueous liquid preparation of claim 26, wherein the stable aqueous liquid preparation consists essentially of: (a) 2-amino-3-(4- bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof, wherein the hydrate is at least one selected from a 1/2 hydrate, 1 hydrate, and 3/2 hydrate; (b) tyloxapol; (c) boric acid; (d) sodium tetraborate; (e) EDTA sodium salt; (f) benzalkonium chloride; (g) polyvinylpyrrolidone; and (h) sodium sulfite; and wherein the concentration of the 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt is from about 0.02 w/v% to about 0.1 w/v %.

32. (New) A stable aqueous liquid preparation comprising: (a) a first component; and (b) a second component; wherein the first component is 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof, wherein the hydrate is at least one selected from a 1/2 hydrate, 1 hydrate, and 3/2 hydrate; the second component is tyloxapol; wherein said stable liquid preparation is formulated for ophthalmic administration; provided that the liquid preparation does not include mannitol.

33. (New) The aqueous liquid preparation according to claim 32, further comprising a quaternary ammonium salt.

34. (New) The aqueous liquid preparation according to claim 32, wherein the first component is a 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt.

35. (New) The aqueous liquid preparation according to claim 34, wherein the concentration of tyloxapol is from about 0.01 w/v % to about 0.05 w/v % and the concentration of the 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt is from about 0.05 to about 0.2 w/v %.

36. (New) The aqueous liquid preparation according to claim 35, wherein the pH is from about 7.5 to about 8.5.

37. (New) The stable aqueous liquid preparation of claim 32; wherein the stable aqueous liquid preparation consists essentially of: (a) 2-amino-3-(4- bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof, wherein the hydrate is at least one

selected from a 1/2 hydrate, 1 hydrate, and 3/2 hydrate; (b) tyloxapol; (c) boric acid; (d) sodium tetraborate; (e) EDTA sodium salt; (f) benzalkonium chloride; (g) polyvinylpyrrolidone; and (h) sodium sulfite; wherein the concentration of the 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt is from about 0.02 w/v% to about 0.1 w/v %.

38. (New) The stable aqueous liquid preparation of claim 32, wherein the stable aqueous liquid preparation is characterized in that greater than about 90% of the original amount of the first component remains in the preparation after storage at about 60 °C for 4 weeks.

39. (New) The aqueous liquid preparation according to claim 38, further comprising a quaternary ammonium salt.

40. (New) The stable aqueous liquid preparation of claim 38; wherein the stable aqueous liquid preparation is characterized in that greater than about 92% of the original amount of the first component remains in the preparation after storage at about 60 °C for 4 weeks.

41. (New) The aqueous liquid preparation according to claim 38, wherein the concentration of tyloxapol is from about 0.01 w/v % to about 0.05 w/v %; and wherein the first component is a 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt, wherein the concentration of the 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt is from about 0.01 to about 0.2 w/v %.

42. (New) The aqueous liquid preparation according to claim 41, wherein the pH is from about 7.5 to about 8.5.

43. (New) The stable aqueous liquid preparation of claim 38, wherein the stable aqueous liquid preparation consists essentially of: (a) 2-amino-3-(4- bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof, wherein the hydrate is at least one selected from a 1/2 hydrate, 1 hydrate, and 3/2 hydrate; (b) tyloxapol; (c) boric acid; (d) sodium tetraborate; (e) EDTA sodium salt; (f) benzalkonium chloride; (g) polyvinylpyrrolidone; and (h) sodium sulfite; wherein said liquid preparation is formulated for ophthalmic administration; and

wherein the concentration of the 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt is from about 0.02 w/v% to about 0.1 w/v %.

44. (New) The aqueous liquid preparation of claim 19, wherein the aqueous liquid preparation further satisfies the preservative efficacy standard of EP-criteria B of the European Pharmacopoeia.

45. (New) The aqueous liquid preparation of claim 26, wherein the aqueous liquid preparation further satisfies the preservative efficacy standard of EP-criteria B of the European Pharmacopoeia.

46. (New) The aqueous liquid preparation of claim 32, wherein the aqueous liquid preparation further satisfies the preservative efficacy standard of EP-criteria B of the European Pharmacopoeia.

47. (New) The aqueous liquid preparation of claim 38, wherein the aqueous liquid preparation further satisfies the preservative efficacy standard of EP-criteria B of the European Pharmacopoeia.

48. (New) The aqueous liquid preparation of claim 40, wherein the aqueous liquid preparation further satisfies the preservative efficacy standard of EP-criteria B of the European Pharmacopoeia.

REMARKS

The present application is a divisional application of Serial No. 13/353,653.

Original claims 1-18 are canceled without prejudice and new claims 19-48 are added.

I. SUPPORT FOR NEW CLAIMS

New claims 19-48 are supported by the original specification and claims.

New claim 19 is supported by original claims 1 and 3; page 7 lines 14-15 and lines 26-28; page 8 lines 16-18; and Experimental Example 1.

New claim 20 is supported by the paragraph bridging pages 3-4.

New claim 21 is supported by page 8 lines 6-10.

New claims 22-23 are supported by page 11 lines 1-6; and page 8 lines 19-26.

New claim 24 is supported by page 6 lines 8-10.

New claim 25 is supported by the compositions of Tables 1 and 2 and page 12 line 23. Note that sodium tetraborate is known as borax and EDTA sodium salt is known as sodium edetate.

New claim 26 is supported as noted above and further supported by Table 2 on page 17 to page 18 line 7.

New claim 27 is supported as noted above.

New claim 28 is supported as noted above and further supported by Table 2.

News claims 29-31 are supported as noted above.

New claim 32 is supported as noted above and further supported by page 12 line 14.

New claims 33-43 are supported as noted above.

New claims 44-48 are supported by Experimental Example 3 on pages 18-22 of the specification.

II. THE SUBJECT MATTER OF NEW CLAIMS 19-48 IS PATENTABLE

Applicant respectfully submits that the subject matter of new claims 19-48 is patentable over the prior art, particularly U.S. Patent No. 5,603,929 to Desai et al. ("Desai").

As an initial matter, Applicant notes that amendments and/or arguments made in the parent applications of the present case to distinguish the prior art do not carry forward and should

not apply to the claims in this application.[1] *See, Hakim v. Cannon Avent Gp., plc*, 479 F.3d 1313 (Fed. Cir. 2007) (permitting rescission of disclaimer and recapture of disclaimed scope so long as that rescission is made clear on the record). The present claims are different and do not, for example, recite the limitation that "when a quaternary ammonium compound is included in said liquid preparation, the quaternary ammonium compound is limited to benzalkonium chloride."

Desai does not disclose the currently claimed composition, with the ingredients combined as recited in the claims. Indeed, one skilled in the art would have interpreted Desai, at a time before applicant's invention, as disclosing a narrow and specific composition that differs significantly from that currently claimed by Applicant.

Desai's objective is to provide a preservative system, the efficacy of which is not degraded or reduced in the presence of an acidic drug (such as diclofenac) that is incompatible with positively charged preservatives. (Desai, column 1, lines 27-34, and column 2, lines 10-14.) Desai stated that its objective was achieved by combining a polymeric quaternary ammonium compound (also known as "polyquat") and boric acid. (Desai, column 2, lines 18-22.) The specification of the Desai patent presented preservative efficacy data for only one formulation (Formulation A). But in addition to a polyquat and boric acid, Formulation A also contained mannitol. (Desai, Example 1, column 4, lines 15-33.) During prosecution, Desai submitted a declaration providing comparative data to show that only the formulation having polyquat-1, though it also contained boric acid and mannitol, satisfied the preservative efficacy criteria, whereas formulations having benzalkonium chloride or benzothenium bromide did not. (Desai's Declaration dated 2/26/1996, Table 2, a copy of which is attached hereto) Desai made a statement regarding the role of mannitol in his compositions, contending it did not have any significant effect on preservative efficacy. (Desai's Supplemental Declaration, dated 7/2/1996, a copy of which is attached hereto) Those skilled in the art, however, would have had a much different understanding of Desai's disclosure and the role of mannitol prior to the time of the present invention.

That Desai's formulation satisfies the preservative efficacy was not due solely to polyquat-1 and boric acid, but to the combination of polyquat-1, boric acid, and mannitol. It had

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[1] The parent applications are Serial No. 13/353,653, filed January 19, 2012, and Serial No. 10/525,006, filed March 28, 2005, now issued as U.S. Patent No. 8,129,431.

been known even before Desai[2] that borate/polyol complexes worked as preservative systems. *See, e.g.*, U.S. Patent No. 5,342,620 to Chowhan, cited by the examiner of the Desai's patent. Borate/polyol complexes enhance the preservative efficacy of a weak preservative, or a preservative amount, that otherwise would not satisfy the preservative efficacy standards. (Chowhan '620, column 1, line 67 to column 2, line 7.) Reading the Desai patent with the knowledge available in the art before Applicant's invention, the skilled artisan would have recognized that the borate/polyol complex, as a whole, contributed to increase the preservative efficacy of polyquat-1—not just boric acid.

Indeed, at the time Desai filed his application for patent, it was already known that mannitol acted to enhance the preservative efficacy of a weak preservative. For example, U.S. Patent No. 5,505,953 issued to Chowhan ("Chowhan '953") provided a comparison of the preservative efficacy of formulations with and without mannitol. (Chowhan '953, column 9, line 15 to column 10, line 26.) The formulations without mannitol failed to meet the British Pharmacopeia (1988) standards. (Chowhan '953, column 9, lines 44-48, and column 10, lines 21-25.) To the best of Applicant's knowledge, the preservative efficacy acceptance criteria of British Pharmacopeia and European Pharmacopeia are similar. Therefore, Chowhan '620 and Chowhan '953 showed that, without mannitol, Desai's objective of meeting the preservative efficacy standard of both US Pharmacopeia XXII and European Pharmacopeia would not have been achieved.

Applicant has experimental results that corroborate what those skilled in the art already knew at the time of Desai and certainly before Applicant's invention: 1) that without mannitol, Desai's combination of only polyquat-1, at a concentration typically used in ophthalmic formulations, and boric acid does not satisfy preservative efficacy criteria, even for the US Pharmacopeia, and 2) that the Desai patent would have been interpreted as requiring the presence of mannitol in addition to boric acid to achieve the touted preservative efficacy.

In this regard, Applicant presents Tables 1 and 2. Table 1 provides the compositional details of six diclofenac formulations, some of which contain mannitol with polyquat-1 and boric acid, and some of which do not contain mannitol. Table 2 provides the preservative efficacy of the preservative in each formulation in Table 1.

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[2] Desai published in February 1997, well before the present application's Japanese priority filing in January 2003.

In Table 1, DBP-1 corresponds closely to Desai's Formulations B and C. It also contains 3.5%w/v of mannitol, whereas Formulation B of Desai contains 1.6 %w/v of mannitol. The 0.005% w/v of polyquat-1 used in Desai's Formulations B and C, as well as in DBP-1, is a typical concentration for this preservative. Desai's Formulation A, on the other hand, has a much higher concentration—4% polyquat-1, a level not typically used in commercial ophthalmic products. Conducting the experiments, therefore, at 0.005% polyquat-1 more effectively shows the importance of mannitol in achieving Desai's stated purpose.

DBP-2 is the same as DBP-1, except it had a pH of 7.8 to discern any effect of pH.

DBP-3 and DBP-4 correspond to DBP-1 and DBP-2, respectively, without mannitol. The results for these formulations show the requirement of mannitol in Desai's formuation.

DBP-5 and DBP-6 correspond to DBP-1 and DBP-2, respectively, without mannitol, but with tyloxapol. Tyloxapol is not a polyol but a polyether.

Table 1. Diclofenac/boric acid/polyol matrix

Ingredient	DBP-1 (%w/v)	DBP-2 (%w/v)	DBP-3 (%w/v)	DBP-4 (%w/v)	DBP-5 (%w/v)	DBP-6 (%w/v)
Sodium Diclofenac	0.1	0.1	0.1	0.1	0.1	0.1
HPMC (E4M)	0.1	0.1	0.1	0.1	0.1	0.1
Tromethamine	2.0	2.0	2.0	2.0	2.0	2.0
Boric Acid	1.2	1.2	1.2	1.2	1.2	1.2
Vitamin E TPGS	3.0	3.0	3.0	3.0	3.0	3.0
Mannitol	3.5	3.5	---	---	---	---
Polyquaternium-1	0.005	0.005	0.005	0.005	0.005	0.005
Tyloxapol	---	---	---	---	0.02	0.02
HCl/NaOH	pH to 7.4	pH to 7.8	pH to 7.4	pH to 7.8	pH to 7.4	pH to 7.8
Purified Water	qs to 100%	qs to 100%	qs to 100%	qs to 100%	qs to 100%	qs to 100%

Table 2 is a collection of tables presenting the preservative efficacy testing results for each of the foregoing formulations.

Table 2. Preservative Efficacy Testing Results

DBP-1: Diclofenac + Mannitol + PQ-1 pH 7.4

Organism	Time Intervals						
	0 hr	6 hr	24 hr	48 hr	7 day	14 day	28 day
A. brasiliensis	0.02	0.06	2.12	2.99	3.10	~3.79	~3.42
C. Albicans	1.01	2.99	>4.51	>4.51	>4.51	>4.51	>4.51
E. coli	2.65	>4.24	>4.24	>4.24	>4.24	>4.24	>4.24
S. aureus	~3.43	>4.49	>4.49	>4.49	>4.49	>4.49	>4.49
P. aeruginosa	>4.64	>4.64	>4.64	>4.64	>4.64	>4.64	>4.64

DBP-2: Diclofenac + Mannitol + PQ-1 pH 7.8

Organism	Time Intervals						
	0 hr	6 hr	24 hr	48 hr	7 day	14 day	28 day
A. brasiliensis	0.05	0.09	1.35	2.82	2.28	2.39	2.59
C. Albicans	0.83	3.06	>4.51	>4.51	>4.51	>4.51	>4.51
E. coli	3.06	>4.24	>4.24	>4.24	>4.24	>4.24	>4.24
S. aureus	~3.52	>4.49	>4.49	>4.49	>4.49	>4.49	>4.49
P. aeruginosa	>4.64	>4.64	>4.64	>4.64	>4.64	>4.64	>4.64

DBP-3: Diclofenac + PQ-1 pH 7.4 (No Mannitol)

Organism	Time Intervals						
	0 hr	6 hr	24 hr	48 hr	7 day	14 day	28 day
A. brasiliensis	0.03	0.34	2.01	~4.01	3.05	2.95	2.61
C. Albicans	~3.48	>4.51	>4.51	>4.51	>4.51	>4.51	>4.51

E. coli	~3.11	>4.24	>4.24	>4.24	>4.24	>4.24	>4.24
S. aureus	~3.37	>4.49	>4.49	>4.49	>4.49	>4.49	>4.49
P. aeruginosa	>4.64	>4.64	>4.64	>4.64	>4.64	>4.64	>4.64

DBP-4: Diclofenac + PQ-1 pH 7.8 (No Mannitol)

Organism	Time Intervals						
	0 hr	6 hr	24 hr	48 hr	7 day	14 day	28 day
A. brasiliensis	0.01	0.93	2.04	3.04	2.12	1.90	0.97
C. Albicans	>4.51	>4.51	>4.51	>4.51	>4.51	>4.51	>4.51
E. coli	~3.31	>4.24	>4.24	>4.24	>4.24	>4.24	>4.24
S. aureus	~3.79	>4.49	>4.49	>4.49	>4.49	>4.49	>4.49
P. aeruginosa	>4.64	>4.64	>4.64	>4.64	>4.64	>4.64	>4.64

DBP-5: Diclofenac + Tyloxapol + PQ-1 pH 7.4

Organism	Time Intervals						
	0 hr	6 hr	24 hr	48 hr	7 day	14 day	28 day
A. brasiliensis	0.06	1.19	2.21	2.96	3.06	2.93	1.08
C. Albicans	~3.32	>4.51	>4.51	>4.51	>4.51	>4.51	>4.51
E. coli	2.73	>4.24	>4.24	>4.24	>4.24	>4.24	>4.24
S. aureus	3.40	>4.49	>4.49	>4.49	>4.49	>4.49	>4.49
P. aeruginosa	~4.16	>4.64	>4.64	>4.64	>4.64	>4.64	>4.64

DBP-6: Diclofenac + Tyloxapol + PQ-1 pH 7.8

Organism	Time Intervals						
	0 hr	6 hr	24 hr	48 hr	7 day	14 day	28 day
A. brasiliensis	0.01	1.03	2.70	2.98	2.05	1.95	1.34
C. Albicans	>4.51	>4.51	>4.51	>4.51	>4.51	>4.51	>4.51
E. coli	~3.43	>4.24	>4.24	>4.24	>4.24	>4.24	>4.24
S. aureus	~3.69	>4.49	>4.49	>4.49	>4.49	>4.49	>4.49
P. aeruginosa	>4.64	>4.64	>4.64	>4.64	>4.64	>4.64	>4.64

The following Table 3 (from the Desai patent) shows the criteria needed to pass the preservative efficacy testing under US Pharmacopeia ("USP"), European Pharmacopeia A ("EP-A"), and European Pharmacopeia B ("EP-B"). EP-A has the most stringent criteria.

Table 3. Preservative Efficacy Acceptance Criteria

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

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

In the results presented in Table 2, *A. brasiliensis* and *C. Albicans* are fungi, and *E. Coli*, *S. aureus*, and *P. Aeruginosa* are bacteria. The preservative efficacy against fungi, especially *A. brasiliensis,* is the most difficult to meet. If the preservative efficacy fails for any one microorganism, the formulation does not meet the preservation efficacy criteria.

Generally speaking, a lower pH of 7.4 is more effective than a pH of 7.8. However, whether a formulation meets the preservative efficacy criteria does not depend on pH in the range of 7.4-7.8.

Only formulations containing all three ingredients, polyquat-1, boric acid, and mannitol (DBP-1 and DBP-2), meet all three preservative efficacy criteria required by Desai. None of the formulations without mannitol (DBP-3 through DBP-6) satisfies any preservative efficacy because the population of the fungus *A. brasilensis* shows an increase from the previous time point. As the tables show with regard to the USP and EP-B criteria, the population of *A. brasilensis* at 28 days is higher than at 14 days. Similarly, with respect to the EP-A criteria, the population of *A. brasilensis* at 28 days is higher than at 7 days.

Thus, the data prove what the skilled person would have understood all along when reading the Desai patent: that, without mannitol, the formulations having polyquat-1 and boric acid do not achieve Desai's purpose of satisfying the preservative efficacy of USP XXII and European Pharmacopeia and that, to be operative for its intended purpose, Desai's formulations must contain mannitol.

In view of the foregoing, Desai's formulations would not have rendered the claims of the present application obvious. The Desai formulations are different from those presently claimed, and there is no suggestion to avoid degradation of acidic drugs, such as bromfenac, by using tyloxapol.

III. CONCLUSION

Applicant respectfully submits that claims 19-48 are patentable over the prior art. A favorable action on the merits 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: 2012.11.28 12:02:34 -05'00'

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

WMC/dlk
Washington, D.C. 20005-1503
Telephone (202) 721-8200
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November 28, 2012

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

10/ Declaration

In re: Desai et al.

Serial No. 08/340,763

Filed: November 16, 1994

Group Art Unit: 1502

Examiner: S. Howard

For: PRESERVED OPHTHALMIC DRUG COMPOSITIONS CONTAINING POLYMERIC QUATERNARY AMMONIUM COMPOUNDS

DECLARATION UNDER 37 CFR §1.132

Honorable Commissioner
of Patents and Trademarks
Washington, D.C. 20231

Dear Sir:

I, Suketu D. Desai, Ph.D., hereby say and declare as follows:

1. I received my B.S. in Pharmacy from the University of Bombay in Bombay, India in 1984, my M.S. in Pharmacology from the University of Bombay in 1986, and my Ph.D. in Pharmaceutical Sciences from the University of Arizona, Tucson, Arizona, in 1992. Since 1992, I have worked in the field of ophthalmic product research and development.

2. I have been employed by Alcon Laboratories, Inc. since 1992. My current position at Alcon is Sr. Scientist II in the Drug Delivery Group. I am responsible for designing, synthesizing, and characterizing ophthalmic formulations, including formulations that are required to pass compendia preservative efficacy standards.

3. As a result of my educational and work-related experiences, I am generally knowledgeable in the field of pharmaceutical formulation science, particularly as related to ophthalmic formulations.

4. I am one of the inventors of the subject matter claimed in U.S. Patent Application Serial No. 08/340,763 filed on November 16, 1994, and understand that this Application sets forth claims to ophthalmic compositions comprising a therapeutically effective amount of one or more acidic ophthalmic agents, a preservative-effective amount of a combination of an antimicrobial polymeric quaternary ammonium compound and boric acid, and an ophthalmically acceptable vehicle.

5. I am familiar with the Office Action dated September 26, 1995, in which claims 1-19 and 25 of the pending application were rejected under 35 USC §103 as unpatentable over Chandrasekaran (WO 89/06964) in combination with Chowhan (U.S. Patent No. 5,342,620). I believe that this rejection is based in part on a misunderstanding concerning the nature of the invention and the cited art.

6. As part of my responsibilities at Alcon, I have designed, conducted and reviewed studies to compare the preservative efficacy of Polyquad® (a polymeric quaternary ammonium preservative, also known as "polyquaternium 1") to that of the following conventional ophthalmic preservatives: benzalkonium chloride (a quaternary ammonium compound, but not a polymeric quaternary ammonium compound), benzyldimethyldodecylammonium bromide (a quaternary ammonium compound, but not a polymeric quaternary ammonium compound), sorbic acid, and thimerosal. These studies evaluated the preservative efficacy of combinations of boric acid and the identified preservatives in acidic ophthalmic drug formulations. I am familiar with the results of these studies.

7. Briefly, the formulations identified in Table 1 below were subjected to a preservative efficacy screen based on the United States Pharmacopeia and European Pharmacopeia (Ph.Eur.) preservative efficacy standards for ophthalmic products. These standards are given in the specification at page 8, lines 5-21. The preservative efficacy screen involved inoculating the formulations identified in Table 1 to known levels of the gram-positive bacteria, Staphylococcus aureus (S. aureus); the gram-negative bacteria, Pseudomonas aeruginosa (P. aeruginosa); and the mold, Aspergillus niger, (A. niger). These inoculated formulations were then sampled at specified intervals of 6 hr, 24 hr, and 7 days to determine whether the antimicrobial preservative system present in the formulation was capable of killing or inhibiting the growth of organisms purposely introduced into the formulation. The magnitude of antimicrobial activity of the formulation determined compliance with the USP and Ph.Eur. preservative efficacy standards for ophthalmic products. The results of these screening tests are presented in Table 2 below.

Table 1: Formulation Ingredients

Formulation Preservative	A Benzalkonium Chloride	B Benzyldimethyl-dodecylammonium bromide	C Polyquaternium 1	D Sorbic Acid	E Thimerosal
	Composition (% w/w)				
Sodium Diclofenac	0.1	0.1	0.1	0.1	0.1
Vitamin E TPGS	3	3	4	3	3
Preservative	0.01	0.0125	0.001	0.2	0.005
Boric Acid	1.2	1.2	1.2	1.2	1.2
HPMC	0.1	0.1	---	---	---
EDTA	0.1	---	---	---	0.1
Mannitol	4	1	3.5	1.2	3.5
HCl/NaOH	q.s. to pH 7.4	q.s. to pH 7.4	q.s. to pH 7.4	q.s. to pH 7.4	q.s. to pH 7.4
Purified Water	q.s. to 100%	q.s. to 100%	q.s. to 100%	q.s. to 100%	q.s. to 100%

Vitamin E TPGS: Vitamin E Tocopheryl Polyethylene Glycol 1000 Succinate
HPMC: Hydroxypropyl methyl cellulose
EDTA: edetic acid or its disodium salt

Table 2: Preservative Efficacy Results For Formulations of Table 1

	Preservative Efficacy Screen Results		
FORMULATION of Example 1	**USP**	**Ph. Eur. A**	**Ph. Eur. B**
A (Benzalkonium chloride)	Fail	Fail	Fail
B (Benzyldimethyldodecyl-ammonium bromide)	Fail	Fail	Fail
C (Polyquaternium 1)	Pass	Pass	Pass
D (Sorbic Acid)	Fail	Fail	Fail
E (Thimerosal)	Pass	Fail	Fail

8. The results shown in Table 2 above demonstrate the disparity between the preservative efficacy of polquaternium 1, a polymeric quaternary ammonium antimicrobial compound, and other, conventional, preservatives of the type disclosed or suggested by the WO 89/06964 and the Chowhan references. In fact, the results show that, among the combinations tested, only the combination of polyquaternium 1 and boric acid was able to effectively preserve the indicated formulation of an acidic ophthalmic drug such that the preservative efficacy standards of the U.S. and Ph.Eur. were met. (These preservative efficacy standards are listed in the Specification at p. 8, lines 5 - 21.) Moreover, only one of the formulations containing conventional ophthalmic preservatives was able to pass even the U.S. preservative efficacy standards (the formulation containing thimerosal). This disparity in results is not suggested by either the WO 89/06964 or the Chowhan references, alone or in combination.

9. I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further, that these statements were made with the knowledge that wilful false statements and the like so made are punishable by fine, 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 therefrom.

Suketu D. Desai, Ph.D. Date: 2/26/96

Attorney Docket No. 1436

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3. I can further explain the formulations which were tested in the original Declaration. These formulations are presented in Table 1 of the original Declaration. The "Vitamin E TPGS" ingredient listed in Table 1 is present in Formulations A, B, D, and E in an amount equal to 3% (w/w), whereas Formulation C contains 4% (w/w). Formulations A, B, C, D, and E in Table 1 also possess different amounts of the "Mannitol" ingredient, ranging from 1 to 4 % (w/w).

4. Neither the "Vitamin E TPGS" nor the "Mannitol" ingredients listed in Table 1 are believed to have any significant effect on the preservative efficacy of the respective formulations. The "Vitamin E TPGS" ingredient is a comfort-enhancing agent which also assists in solubilizing the tested active, sodium diclofenac. The "Mannitol" ingredient is a tonicity-adjusting agent of the type commonly used in ophthalmic preparations to make the preparations match or nearly match the tonicity of the lacrimal fluid. Neither the discrepancy in "Vitamin E TPGS" concentration nor the discrepancy in "Mannitol" concentration among Formulations A-E in Table 1 of the original Declaration are believed to effect the conclusion that is drawn from the data presented in the original Declaration, namely that, unlike the other preservatives tested in combination with boric acid, Applicants combination of an antimicrobial polymeric quaternary ammonium compound and boric acid is effective in preserving acidic ophthalmic agents.

5. I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further, that these statements were made with the knowledge that wilful false statements and the like so made are punishable by fine, 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 therefrom.

Suketu D. Desai, Ph.D.

Date: 07/02/96

Attorney Docket No. 1436

PTO/SB/424 (12-11)

CERTIFICATION AND REQUEST FOR PRIORITIZED EXAMINATION UNDER 37 CFR 1.102(e) (Page 1 of 1)

First Named Inventor:	Shirou SAWA	Nonprovisional Application Number (if known):	
Title of Invention:	AQUEOUS LIQUID PREPARATION CONTAINING 2-AMINO-3-(4-BROMOBENZOYL)PHENYLACETIC ACID		

APPLICANT HEREBY CERTIFIES THE FOLLOWING AND REQUESTS PRIORITIZED EXAMINATION FOR THE ABOVE-IDENTIFIED APPLICATION.

1. The processing fee set forth in 37 CFR 1.17(i), the prioritized examination fee set forth in 37 CFR 1.17(c), and if not already paid, the publication fee set forth in 37 CFR 1.18(d) have been filed with the request. The basic filing fee, search fee, examination fee, and any required excess claims and application size fees are filed with the request or have been already been paid.

2. The application contains or is amended to contain no more than four independent claims and no more than thirty total claims, and no multiple dependent claims.

3. The applicable box is checked below:

I. ☑ Original Application (Track One) - Prioritized Examination under § 1.102(e)(1)

i. (a) The application is an original nonprovisional utility application filed under 35 U.S.C. 111(a). This certification and request is being filed with the utility application via EFS-Web.

---OR---

(b) The application is an original nonprovisional plant application filed under 35 U.S.C. 111(a). This certification and request is being filed with the plant application in paper.

ii. An executed oath or declaration under 37 CFR 1.63 is filed with the application.

II. ☐ Request for Continued Examination - Prioritized Examination under § 1.102(e)(2)

i. A request for continued examination has been filed with, or prior to, this form.
ii. If the application is a utility application, this certification and request is being filed via EFS-Web.
iii. The application is an original nonprovisional utility application filed under 35 U.S.C. 111(a), or is a national stage entry under 35 U.S.C. 371.
iv. This certification and request is being filed prior to the mailing of a first Office action responsive to the request for continued examination.
v. No prior request for continued examination has been granted prioritized examination status under 37 CFR 1.102(e)(2).

/Warren M. Cheek/ Digitally signed by /Warren M. Cheek/
DN: cn=/Warren M. Cheek/, o, ou, email=wcheek@wenderoth.com, c=US
Date: 2012.11.28 12:49:02 -05'00'

Signature /Warren M. Cheek/	Date November 28, 2012
Name (Print/Typed) Warren M. Cheek	Practitioner Registration Number 33,367

Note: *Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required in accordance with 37 CFR 1.33 and 11.18. Please see 37 CFR 1.4(d) for the form of the signature. If necessary, submit multiple forms for more than one signature, see below*.*

☐ *Total of 1 forms are submitted.

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.

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_5420

Filed as Large Entity

Track I Prioritized Examination - Nonprovisional Application under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Utility application filing	1011	1	390	390
Utility Search Fee	1111	1	620	620
Utility Examination Fee	1311	1	250	250
Request for Prioritized Examination	1817	1	4800	4800
Pages:				
Claims:				
Claims in excess of 20	1202	10	62	620
Miscellaneous-Filing:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Publ. Fee- early, voluntary, or normal	1504	1	300	300
Processing Fee, except for Provis. apps	1808	1	130	130
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Miscellaneous:				
		Total in USD ($)		**7110**

Electronic Acknowledgement Receipt

EFS ID:	14325791
Application Number:	13687242
International Application Number:	
Confirmation Number:	1577
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_5420
Receipt Date:	28-NOV-2012
Filing Date:	
Time Stamp:	13:50:13
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Credit Card
Payment was successfully received in RAM	$7110
RAM confirmation Number	205
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	AttachA1_Trans.pdf	233839 403ec4f9902809724352d3f3d8d4f467b373cd8e	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	Application Data Sheet	AttachA2_Ads.pdf	1001648 5996ff89e3c103c6ce6a420347ce692c8c449475	no	6

Warnings:

Information:

3		AttachB_Spec.PDF	983119 3464c9a8a607b953339b5b78f93a495220cf5755	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:

4	Oath or Declaration filed	AttachC1_Decl.PDF	87228 883dc538c2b8488d3846553f6db19d5b6ed23ef8	no	2

Warnings:

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

Information:

5	Power of Attorney	AttachC2_Poa.PDF	166894 e3a80da4d3d16f510bd5f3910bc52aa5a41bab64	no	2

Warnings:

The PDF file has been signed with a digital signature and the legal effect of the document will be based on the contents of the file not the digital signature.					
Information:					
6	Information Disclosure Statement (IDS) Form (SB08)	AttachD1_Ids.pdf	411745 3b0d9518c7d171655a5e139868854bc573e15796	no	6
Warnings:					
Information:					
This is not an USPTO supplied IDS fillable form					
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.					
7	Preliminary Amendment	AttachE_Pa.PDF	982181 a5569125852288dc50a218b37eebc1eb241b85ba	no	24
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:					
8	TrackOne Request	AttachF.pdf	638958 d271243ec0325d1207405c004001f66010d13957	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:					
9	Fee Worksheet (SB06)	fee-info.pdf	42193 8484f84dff4a289b42c421c49f9ff0e929248eba	no	2
Warnings:					
Information:					
			Total Files Size (in bytes):	4547805	

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.

DECLARATION FOR UTILITY OR DESIGN APPLICATION

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

As the below named inventor, I hereby declare that:

This declaration is directed to:

[X] The attached application, or

[ ] United States application or PCT international application number filed on .

The above-identified application was made or authorized to be made by me.

I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.

I hereby acknowledge that any willful false statement made in this declaration is punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both.

Note to Inventor: 37 C.F.R. § 1.63(c) states: "A person may not execute an oath or declaration for an application unless that person has reviewed and understands the contents of the application, including the claims, and is aware of the duty to disclose to the Office all information known to the person to be material to patentability as defined in § 1.56."

Inventor (Legal Name): **Shirou SAWA**

Signature: Shirou Sawa Date: Nov. 16. 2012

Note: Use an additional form for each additional inventor.

Wenderoth, Lind & Ponack, LLP
Attorney Docket No.: 2012_5420/WMC/01736

Modified PTO/AIA/01 (06-12)

DECLARATION FOR UTILITY OR DESIGN APPLICATION

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

As the below named inventor, I hereby declare that:

This declaration is directed to:

[X] The attached application, or

[ ] United States application or PCT international application number filed on .

The above-identified application was made or authorized to be made by me.

I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.

I hereby acknowledge that any willful false statement made in this declaration is punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both.

Note to Inventor: 37 C.F.R. § 1.63(c) states: "A person may not execute an oath or declaration for an application unless that person has reviewed and understands the contents of the application, including the claims, and is aware of the duty to disclose to the Office all information known to the person to be material to patentability as defined in § 1.56."

Inventor (Legal Name): **Shuhei FUJITA**

Signature: Shuhei Fujita Date: 2012.11.19

Note: Use an additional form for each additional inventor.

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
13/687,242	11/28/2012	

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	390
☐ 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	390

APPLICATION AS AMENDED – PART II

AMENDMENT 11/28/2012	(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))	* 30	Minus	** 30	= 0	X $ =		OR	X $62=	0
Independent (37 CFR 1.16(h))	* 2	Minus	***3	= 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:
/FELICIA ALLEN-JENKINS/