[0019]

Although the content 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 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.

[0020]

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.

[0021]

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.

[0022]

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.

[0023]

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.

[0024]

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.

[0025]

The pH of the aqueous liquid preparation of the present invention is adjusted to about 7 to 9, preferably about 7.5 to 8.5.

[0026]

So long as the purpose of the present invention is achieved, other same or different kind of active ingredients may be appropriately added.

[0027]

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.

[0028]

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.

[0029]

The aqueous liquid preparation of the present invention, for example, 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.

[0030]

[Examples]

The present invention is illustrated by way of the following Experimental Examples and Working Examples, but the present invention is not restricted to these Examples.

[0031]

Experimental Example 1: Stability test of sodium 2-amino-3-(4-bromobenzoyl)phenylacetate

(Experimental Method)

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.

[0032]

[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
60°C-4W	51.3	63.7	73.8	89.6

[0033]

The remaining rate (%) in the above Table 1 indicates values obtained by correcting the content of sodium 2-amino-3-(4-bromobenzoyl)phenylacetate taking into account 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, sodium 2-amino-3-(4-bromobenzoyl)phenylacetate in the composition containing 0.02 w/v % of tyloxapol is more stable

than that in the composition containing 0.15 w/v % of tyloxapol.

[0034]

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

(Experimental Method)

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 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 corrected value taking into account moisture vaporization from the container.

[0035]

[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-4W	Remaining rate	92.6	90.9	92.0	93.4	93.1
	pH	8.15	8.16	8.15	8.13	8.14

[0036]

As is apparent from Table 2, the remaining rate of sodium 2-amino-3-(4-bromobenzoyl)phenylacetate in the compositions 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.

[0037]

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.

The results are shown in Table 3.

[0038]

[Table 3]

Table 3-1

A−04	Inoculum count	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

Table 3-2

A−05	Inoculum count	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

Table 3-3

A−07	Inoculum count	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]

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 [1)], and those of compositions A-05 and A-07 were found to be compatible with EP-criteria B [2)].

[0040]

1) EP(European Pharmacopoeia)-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.

2) 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.

[0041]

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 edentate	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.

[0042]

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.

[0043]

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.

[0044]

[Effect of the Invention]

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.).

[Name of Document] Abstract

[Abstract]

[Problem]

To provide an aqueous liquid preparation containing stabilized 2-amino-3-(4-bromobenzoyl)phenylacetic acid or its pharmacologically acceptable salt or a hydrate thereof, which is stable and exhibits a sufficient preservative effect.

[Means for solving the problem]

An aqueous liquid preparation containing 2-amino-3-(4-bromobenzoyl)phenylacetic acid or its pharmacologically acceptable salt or a hydrate thereof and an alkyl aryl polyether alcohol type polymer such as tyloxapol, or a polyethylene glycol fatty acid ester such as polyethylene glycol monostearate.

[Chosen Drawing] None

Applicant's History Information

Identification Number: [000199175]

1. Date of Change August 22, 1990
[Reason for Change] Newly recorded
Address: 5-8, Hiranomachi 2-chome, Chuo-ku, Osaka-shi, OSAKA
Name: SENJU PHARMACEUTICAL CO., LTD.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of	:	Attorney Docket No. 2005_0232A
Shirou SAWA et al.	:	**Confirmation No. 1756**
Serial No. 10/525,006	:	Group Art Unit 1614
Filed March 28, 2005	:	Examiner Donna A. Jagoe
AQUEOUS LIQUID PREPARATION CONTAINING 2-AMINO-3-(4-BROMOBENZOYL)PHENYLACETIC ACID	:	**Mail Stop: RCE**

PATENT OFFICE FEE TRANSMITTAL FORM

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

Sir:

Attached hereto is a Credit Card Payment Form authorizing payment in the amount of $940.00 to cover Patent Office fees relating to filing the following attached papers:

Request for Continued Examination (RCE)	$810.00
Petition for Extension of Time	$130.00

Respectfully submitted,

Shirou SAWA et al.

By _____
Warren M. Cheek
Registration No. 33,367
Attorney for Applicants

WMC/dlk
Washington, D.C. 2005-1503
Telephone (202) 721-8200
Facsimile (202) 721-8250
October 5, 2009

The Commissioner is authorized to charge any deficiency or to credit any overpayment associated with this communication to Deposit Account No. 23-0975.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of	:	Attorney Docket No. 2005_0232A
Shirou SAWA et al.	:	**Confirmation No. 1756**
Serial No. 10/525,006	:	Group Art Unit 1614
Filed March 28, 2005	:	Examiner Donna A. Jagoe
AQUEOUS LIQUID PREPARATION CONTAINING 2-AMINO-3-(4-BROMOBENZOYL)PHENYLACETIC ACID	:	**Mail Stop: RCE**

PETITION FOR EXTENSION OF TIME

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

Sir:

Petition hereby is made for a one month extension of time to respond to the communication of June 3, 2009.

The fee of $130.00 is

(X) to be charged to Credit Card (per attached Credit Card Authorization Form).

() to be charged to Deposit Account No. 23-0975. A duplicate copy of this Petition is enclosed.

() Small entity status of this application is established by a Small Entity Status Assertion which

- () is enclosed.
- () has been previously submitted.
- () has been previously asserted.

Respectfully submitted,
Shirou SAWA et al.

By _____
Warren M. Cheek
Registration No. 33,367
Attorney for Applicants

WMC/dlk
Washington, D.C. 20005-1503
Telephone (202) 721-8200
Facsimile (202) 721-8250
October 5, 2009

10/06/2009 SZEWDIE1 00000028 10525006
01 FC:1801 810.00 OP

The Commissioner is authorized to charge any deficiency or to credit any overpayment associated with this communication to Deposit Account No. 23-0975.

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number	Filing Date	☒ To be Mailed
10/525,006	03/28/2005	

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY ☐ RATE ($)	SMALL ENTITY ☐ FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =		OR	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =			X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT	10/05/2009	(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))	* 41	Minus	** 45	= 0	X $ =		OR	X $52=	0
	Independent (37 CFR 1.16(h))	* 7	Minus	***7	= 0	X $ =		OR	X $220=	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:
/ANGELA D. JOHNSON/

This collection of information is required by 37 CFR 1.16. 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, 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.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

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.
10/525,006	03/28/2005	Shirou Sawa	2005_0232A	1756

513 7590 06/03/2009

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

EXAMINER	
JAGOE, DONNA A	

ART UNIT	PAPER NUMBER
1614	

MAIL DATE	DELIVERY MODE
06/03/2009	PAPER

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.

Office Action Summary	Application No.	Applicant(s)	
	10/525,006	SAWA ET AL.	
	Examiner	Art Unit	
	Donna Jagoe	1614	

-- 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 *15 January 2009*.

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

3)☐ 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

4)☒ Claim(s) *19-29,31-34,36-51,53-56 and 58-63* is/are pending in the application.

4a) Of the above claim(s) *39,40,61 and 62* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *19-29,31-34,36-38,41-51,53-56,58-60 and 63* is/are rejected.

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

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

Application Papers

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

10)☐ 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).

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

Priority under 35 U.S.C. § 119

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) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/11/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 19-29, 31-34, 36-51, 53-56 and 58-63 are pending in this application.

Claims 39, 40, 61 and 62 are withdrawn from further consideration.

Claims 19-29, 31-34, 36-38, 41-51, 53-56, 58-60 and 63 are rejected.

Applicants' arguments filed January 15, 2009 have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Change of Examiner

The examiner assigned to the instant application has changed. The new examiner is Donna Jagoe. Contact information is provided at the end of this Office Action.

Priority

As recited in the Office Action dated September 27, 2007, Applicant is reminded that a certified translation has not been proved for the claim to foreign priority of JP2003-012427, filed 1/21/2003. Since no translation has been provided, prior art

dates have been determined with reference to the priority date for the PCT application date, PCT/JP04/00350, filed 1/16/2004.

Claim Rejections - 35 USC § 112

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

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

Claims 19-29, 31-34, 36-38, 41-51, 53-56, 58-60 and 63, are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 19 and 41 recite an aqueous liquid preparation comprising at least 2-amino-3-(4-bromobenzoyl)phenylacetic acid (bromfenac) and an alkyl aryl polyether alcohol type polymer or polyethylene glycol fatty acid ester “wherein said liquid preparation is in the form of an eye drop”. It is unclear what is meant by “in the form of an eye drop. Is this aqueous liquid preparation in a container shaped like an eye drop? It is suggested that the claim be amended to recite "wherein said liquid preparation is formulated for ophthalmic administration".

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 19-29, 31-34, 36-38, 41-51, 53-56, 58-60 and 63 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hellberg et al. (US 5,998,465; 1999) and

Nolan, et al. ("The topical anti-inflammatory and analgesic properties of bromfenac in rodents; Agents and Actions; 1988 Aug; 25(1-2):77-85; cited with previous Interview Summary).

Hellberg teaches pharmaceutical compositions of anti-inflammatory compounds (abstract); the compounds include a non-steroidal anti-inflammatory moiety (NSAIA) and an antioxidant moiety linked through an ester bond formed by the carboxylic acid moiety of the NSAIA (col. 2, lines 20-24); NSAIA moieties include bromfenac (col. 3, line 57; claim 5); examples 2 and 3 (col. 11) teach topical ophthalmic formulations useful for treating inflammation, both of these formulations include tyloxapol at 0.01-0.05 w/v %, HPMC (thickener), benzalkonium chloride (preservative), edetate disodium (chelating agent) (col. 11, Examples 2-3); the pH is adjusted to 7.4 (about 7.5; col. 11, line 64); topical formulations administered by drops (eye drops; col. 10, lines 15-18). Hellberg does not teach bromfenac (only the ester of bromfenac). Nolan teaches bromfenac (the sodium salt, sesquihydrate form) was effective as a topical analgesic at concentrations of 0.1-0.32 % in mice and more potent than the other drugs tested (abstract). It would have been obvious for one of ordinary skill in the art at the time of the invention to substitute bromfenac, taught by Nolan for the compounds of Hellberg in the example formulation giving formulations of the instant claims and to select concentrations of bromfenac sodium, sesquihydrate of 0.1, about 0.2 and about 0.32 %, in the invention of Gamache, since these values have demonstrated efficacy for topical use. It would also have been obvious to adjust the concentration of tyloxapol, to optimize the formulations for the effect would on the solubility and stability of the aqueous

preparations, which would have resulted in the effective tyloxapol concentrations of about 0.02 and 0.3 w/v%, recited in claims 25 and 32. The motivation to substitute bromfenac in the Hellberg formulations would have bee the art-recognized equivalent activity of bromfenac as an anti-inflammatory agent in topical usage. The motivation to adjust concentrations would have been the routine optimization of these topical ophthalmic formulations for anti-inflammatory use in the eye.

Claims 19-29, 31-34 and 36-38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gamache, et al. (WO 01/15677 A2; 03/2001; previously cited) and ISTA Pharmaceuticals ("New Drug Applications: Xibrom", http://www.drugs.com/nda/xibrom_040525.html, accessed online 9/19/2007; previously cited) or Nolan, et al. ("The topical anti-inflammatory and analgesic properties of bromfenac in rodents; Agents and Actions; 1988 Aug; 25(1-2):77-85; provided with Interview Summary).

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). It is noted that instant claim 21 and further dependent claims limit the options for the salt of bromfenac to the sodium salt, and that the specific concentrations recited in dependent claims apply to the sodium salt; the other options (bromfenac or a hydrate of bromfenac) are still viable choices that are part of instant claim 21 claims depending therefrom (which depend on and include the options of claim 20). Gamache teaches bromfenac in the concentration range of claim 20 (which is also an option of claims 21-24 and 31). 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, albeit not the sodium salt concentration limitation of instant claim 22 and further dependent claims, since the claim is drawn to an aqueous liquid preparation, irrespective of how it is prepared. However, the concentration range of 0.01-1.0% overlaps and encompasses the claimed concentration range of the sodium salt of bromfenac instantly claimed.

The ISTA Pharmaceuticals news release demonstrates that products containing 0.1 % bromfenac sodium acquired US marketing rights for Xibrom in May 2002 (were known by others in this country before applicant's priority date, a 35 USC 102(a) date). Nolan teaches bromfenac (the sodium salt, sesquihydrate form) was effective as a topical analgesic at concentrations of 0.1-0.32 % in mice and more potent than the other drugs tested (abstract). It would have been obvious for one of ordinary skill in the art at

the time of the invention to select concentrations of bromfenac sodium, sesquihydrate of 0.1, about 0.2 and about 0.32 %, in the invention of Gamache, since these values have demonstrated efficacy for topical use. 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.

Double Patenting

Claims 19-29, 31-34, 36-38, 41-51, 53-56, 58-60 and 63 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-43 of copending Application No. 11/755662.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the copending application contains claims drawn to method of treating pain and/or inflammation associated with an ocular condition, by administering the aqueous solutions of the instant claims. It would have been obvious to one of ordinary skill in the art at the time of the invention to use the formulations of the instant claims in the methods of the copending application, since the claims recite that the

formulations are eye drops, and the instant abstract also teaches some of the conditions treated of the copending application.

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

Response to Arguments

Applicant asserts that Gamache et al. in view of ISTA or Nolan et al. does not teach the claimed invention because the amended claims require that the aqueous liquid preparation is in the form of an eye drop. In response, please see the rejection supra regarding claims drawn to the composition "in the form of an eye drop". Further, Gamache teaches the composition to be employed intranasally and intraotically. There is nothing differentiating the composition of the instant claims from the composition of Gamache other than the claim that it is "in the form of an eye drop". Drops that are formulated for intranasal use and otic use are sterile and isotonic. The intended use must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. Since the drops of Gamache are capable of performing the intended use, then it meets the claim. Regarding the inclusion of other agents in the drops of Gamache, The claim language *comprising* leaves the claim open for the inclusion of unspecified ingredients, even in major amounts. Applicant asserts that the tyloxapol is only mentioned as being added to an 1B/1D agonist and moxifloxacin in example 4 with no explanation of why it is

included. In response, a reference is not limited to working examples. *In re Fracalossi* 215 USPQ 569 (CCPA 1982). Applicant asserts that Gamache et la. Is silent regarding the alkyl aryl polyether alcohol type polymer or a polyethylene glycol fatty acid ester component according to the claimed eye drop. In response, Gamache et al. teach polysorbate 20, 60, and 80 as a surfactant or co-solvent (see page 12).

Applicant asserts that the intended purpose of the invention disclosed in Hellberg et al. is to provide compounds having anti-inflammatory activity and antioxidant activity and further asserts it would not be obvious to substitute bromfenac. In response, bromfenac is clearly disclosed as a compound that is contemplated for use in the invention of Hellberg et al. (see claims 5 and 19 of the patent). "Products of identical chemical composition (i.e. bromfenac) can not have mutually exclusive properties." A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims (i.e. anti inflammatory and antioxidant activity) are necessarily present. In re Spada, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990) (Applicant argued that the claimed composition was a pressure sensitive adhesive containing a tacky polymer while the product of the reference was hard and abrasion resistant. "The Board correctly found that the virtual identity of monomers and procedures sufficed to support a prima facie case of unpatentability of Spada's polymer latexes for lack of novelty.").

In response to applicant's argument that Hellberg et al. is nonanalogous art, it has been held that a prior art reference must either be in the field of applicant's endeavor or, if not, then be reasonably pertinent to the particular problem with which the

applicant was concerned, in order to be relied upon as a basis for rejection of the claimed invention. See *In re Oetiker*, 977 F.2d 1443, 24 USPQ2d 1443 (Fed. Cir. 1992). In this case, Hellberg et al. teach a composition for intraocular administration comprising inter alia, a compound (bromfenac) and tyloxapol (see examples).

Conclusion

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

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

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Donna Jagoe whose telephone number is (571) 272-

0576. The examiner can normally be reached on Monday through Friday from 8:00 A.M. - 4:30 P.M..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on (571) 272-0718. 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.

Donna Jagoe /D. J./
Examiner
Art Unit 1614

May 30, 2009

/Ardin Marschel/
Supervisory Patent Examiner, Art Unit 1614

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	10525006	SAWA ET AL.
	Examiner	Art Unit
	Thomas, Timothy P	1614

SEARCHED

Class	Subclass	Date	Examiner
514	567	5/30/09	dj
424	486	5/30/09	dj

SEARCH NOTES

Search Notes	Date	Examiner
WEST	9/19/2007	TPT
Google	9/19/2007	TPT
STN Search	9/19/2007	TPT
PubMed	9/19/2007	TPT
Inventor Name Search	9/19/2007	TPT
IDS References	9/19/2007	TPT
PubChem	7/2/2008	TPT
WEST	7/2/2008	TPT
PubMed	7/2/2008	TPT
IDS references	7/2/2008	TPT
WEST see attached search history transcript	5/30/09	dj
GOOGLE advanced scholar search	5/30/09	dj

INTERFERENCE SEARCH

Class	Subclass	Date	Examiner

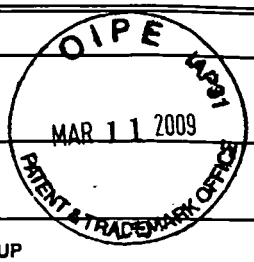
/Donna Jagoe/ Examiner.Art Unit 1614	

U.S. Patent and Trademark Office Part of Paper No. : 20090528

March 11, 2009

Sheet 1 of 1

INFORMATION DISCLOSURE STATEMENT



FORM PTO 1449 (*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: March 11, 2009

ATTY DOCKET NO.	SERIAL NO.
2005_0232A	10/525,006

APPLICANT
Shirou SAWA et al.

FILING DATE	GROUP
March 28, 2005	1614

U.S. PATENT DOCUMENTS

*EXAMINER INITIAL		DOCUMENT NUMBER	DATE	NAME	CLASS	SUBCLASS	FILING DATE IF APPROPRIATE
	AA	5,597,560	1/1997	Bergamini et al.			
	AB						
	AC						
	AD						
	AE						
	AF						
	AG						
	AH						
	AI						

FOREIGN PATENT DOCUMENTS

		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION YES	TRANSLATION NO
	BA	01/15677	3/2001	WO				
	BB	2 013 188	9/1990	CA				
	BC	02/13804	2/2002	WO				
	BD	707 119	9/1995	AU				
	BE							

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

	CA	Notice of Opposition dated February 19, 2009 issued by EPO in connection with the corresponding European patent application and Opposition.
	CB	
	CC	

EXAMINER	/Donna Jagoe/ (05/30/2009)	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.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /D.J./ (05/30/2009)

Google Scholar BETA

Web Images Video News Maps **more »**

bromfenac tyloxapol "eye drop" - 2003 Search

Ad Sc Sc

Scholar

Results **1** - **1** of **1** for **bromfenac tyloxapol "eye drop"**. (**0.06** seconds)

Tip: Try removing quotes from your search to get more results.

Ophthalmic formulation with novel gum composition

SK Singh, P Bandyopadhyay - US Patent App. 10/370,220, 2003 - Google Patents

... After instillation of an **eye-drop**, typically less than 5% of the applied drug penetrates the cornea and reaches intraocular tissues. **...**

Web Search - All 4 versions

bromfenac tyloxapol "eye drop" Search

Google Home - About Google - About Google Scholar

WEST Search History for Application 10525006

Creation Date: 2009053020:27

Query	DB	Op.	Plur.	Thes.	Date
bromfecan	PGPB, USPT, USOC, EPAB, JPAB, DWPI	ADJ	YES		05-30-2009
bromfenac	PGPB, USPT, USOC, EPAB, JPAB, DWPI	ADJ	YES		05-30-2009
tyloxapol	PGPB, USPT, USOC, EPAB, JPAB, DWPI	ADJ	YES		05-30-2009
sterile	PGPB, USPT, USOC, EPAB, JPAB, DWPI	ADJ	YES		05-30-2009
isotonic	PGPB, USPT, USOC, EPAB, JPAB, DWPI	ADJ	YES		05-30-2009
pH	PGPB, USPT, USOC, EPAB, JPAB, DWPI	ADJ	YES		05-30-2009
(bromfenac) and (tyloxapol) and (sterile) and (isotonic) and (pH)	PGPB, USPT, USOC, EPAB, JPAB, DWPI	ADJ	YES		05-30-2009

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of	:	**Confirmation No. 1756**
Shirou SAWA et al.	:	Attorney Docket No. 2005_0232A
Serial No. 10/525,006	:	Group Art Unit 1614
Filed March 28, 2005	:	Examiner Timothy P. Thomas

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:

Pursuant to the provisions of 37 CFR 1.56, 1.97 and 1.98, Applicants request consideration of the references listed on attached form PTO-1449 and any additional information identified below in paragraph 3. A legible copy of each reference listed on the Form PTO-1449 is enclosed, except a copy is not provided for:

[X] each U.S. Patent and U.S. Patent application publication;

[] each reference previously cited in prior parent application Serial No. _____.

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) [X] 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. [X] 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, 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.

3. [] Consideration of the following list of additional information (including any copending or abandoned U.S. application, prior uses and/or sales, etc.) is requested.

4. For each non-English language reference listed on the attached form PTO-1449, reference is made to:

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

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

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

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

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

5. [X] A Notice of Opposition citing one or more of the references is enclosed. References D1 and D7 of the Notice of Opposition are not cited because they are already of record.

6. [] Statement Under 37 CFR 1.704(d)

Each item of information contained in the Information Disclosure Statement was first cited in any communication from a foreign Patent Office in a counterpart application, 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.

The Commissioner is authorized to charge any deficiency or to credit any overpayment associated with this communication to Deposit Account No. 23-0975, with the EXCEPTION of deficiencies in fees for multiple dependent claims in new applications.

Respectfully submitted,

Shirou SAWA et al.

By _____

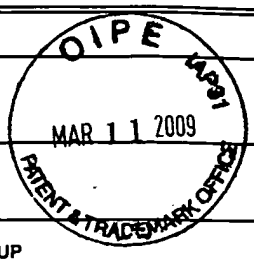
Warren M. Cheek
Registration No. 33,367
Attorney for Applicants

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

March 11, 2009

Sheet 1 of 1

INFORMATION DISCLOSURE STATEMENT



FORM PTO 1449 (*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: March 11, 2009

ATTY DOCKET NO.	SERIAL NO.
2005_0232A	10/525,006

APPLICANT
Shirou SAWA et al.

FILING DATE	GROUP
March 28, 2005	1614

U.S. PATENT DOCUMENTS

*EXAMINER INITIAL		DOCUMENT NUMBER	DATE	NAME	CLASS	SUBCLASS	FILING DATE IF APPROPRIATE
	AA	5,597,560	1/1997	Bergamini et al.			
	AB						
	AC						
	AD						
	AE						
	AF						
	AG						
	AH						
	AI						

FOREIGN PATENT DOCUMENTS

		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION YES	TRANSLATION NO
	BA	01/15677	3/2001	WO				
	BB	2 013 188	9/1990	CA				
	BC	02/13804	2/2002	WO				
	BD	707 119	9/1995	AU				
	BE							

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

	CA	Notice of Opposition dated February 19, 2009 issued by EPO in connection with the corresponding European patent application and Opposition.
	CB	
	CC	

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.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
8 March 2001 (08.03.2001)

PCT

(10) International Publication Number
WO 01/15677 A2

(51) International Patent Classification[7]: A61K 31/00, 31/498, A61P 27/16

(21) International Application Number: PCT/US00/22764

(22) International Filing Date: 18 August 2000 (18.08.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
09/387,358 31 August 1999 (31.08.1999) US

(71) Applicant *(for all designated States except US)*: ALCON LABORATORIES, INC. [US/US]; 6201 South Freeway, Mail Code Q-148, Fort Worth, TX 76134 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: GAMACHE, Daniel, A. [US/US]; 5610 Hunterwood Lane, Arlington, TX 76017 (US). YANNI, John, M. [US/US]; 2821 Donnybrook Drive, Burleson, TX 76028 (US). SHARIF, Najam, A. [US/US]; 7 Courtney Court, Arlington, TX 76015 (US).

(74) Agents: YEAGER, Sally, S. et al.; Alcon Research, Ltd., R & D Counsel, Mail Code Q-148, 6201 South Freeway, Fort Worth, TX 76134 (US).

(81) Designated States *(national)*: AU, BR, CA, CN, JP, MX, PL, TR, US, ZA.

(84) Designated States *(regional)*: European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published:
— *Without international search report and to be republished upon receipt of that report.*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/15677 A2

(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-Hydroxytryptamine1Dβ 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.

(19) Canadian Intellectual Property Office / Office de la Propriété Intellectuelle du Canada

An Agency of Industry Canada / Un organisme d'Industrie Canada

(11) CA 2 013 188 (13) C

(40) 14.03.2000
(43) 28.09.1990
(45) 14.03.2000

(12)

(21) 2 013 188

(22) 27.03.1990

(51) Int. Cl.[5]: A61K 031/71, A61K 031/19, A61K 031/405

(30) 07/329,451 US 28.03.1989

(73) Syntex (U.S.A.) Inc.
3401 Hillview Avenue PALO ALTO XX (US).

(72) Fu, Cherng-Chyi Roger (US).
Lidgate, Deborah M. (US).

(74) DENNISON ASSOCIATES

(54) SYSTEME POUR CONSERVER LES PREPARATIONS OPHTALMIQUES
(54) PRESERVATIVE SYSTEM FOR OPHTHALMIC FORMULATIONS

(57)

Stable, clear, antimicrobially effective, ophthalmic formulations are disclosed which provide an antimicrobially effective preservative. The formulations include an ophthalmologically effective amount of a drug, which is a -COON group-containing non-steroidal anti-inflammatory drug (NSAID) in combination with an antibiotic drug, and a preservative system formed of a quaternary ammonium preservative and a nonionic polyoxyethylated octylphenol surfactant, all in an aqueous vehicle. The preservative system can be used with other formulations which require the preservative to be ophthamologically acceptable and antimicrobially effective. These formulations are useful for treating diseases and/or conditions that are either caused by, associated with or accompanied by inflammatory processes, including, among others, glaucoma, cystoid macular edema, uveitis, diabetic retinopathy and conjunctivitis, or any trauma caused by eye surgery or eye injury. The ophthalmologically acceptable antibiotic is preferably tobramycin which has been found not to interfere with the rate of diffusion of the NSAID. The combination of the NSAID and antibiotic is particularly effective in simultaneously preventing and/or eliminating infection while preventing and/or eliminating inflammation.

OPIC
OFFICE DE LA PROPRIÉTÉ INTELLECTUELLE DU CANADA

CIPO
CANADIAN INTELLECTUAL PROPERTY OFFICE

(12)(19)(CA) **Brevet-Patent**

(11)(21)(C) **2,013,188**
(22) 1990/03/27
(43) 1990/09/28
(45) 2000/03/14

(72) Fu, Cherng-Chyi Roger, US
(72) Lidgate, Deborah M., US
(73) Syntex (U.S.A.) Inc., US

(51) Int.Cl.[5] A61K 31/71, A61K 31/405, A61K 31/19
(30) 1989/03/28 (07/329,451) US

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

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

(57) Stable, clear, antimicrobially effective, ophthalmic formulations are disclosed which provide an antimicrobially effective preservative. The formulations include an ophthalmologically effective amount of a drug, which is a -COOH group-containing non-steroidal anti-inflammatory drug (NSAID) in combination with an antibiotic drug, and a preservative system formed of a quaternary ammonium preservative and a nonionic polyoxyethylated octylphenol surfactant, all in an aqueous vehicle. The preservative system can be used with other formulations which require the preservative to be ophthamologically acceptable and antimicrobially effective. These formulations are useful for treating diseases and/or conditions that are either caused by, associated with or accompanied by inflammatory processes, including, among others, glaucoma, cystoid macular edema, uveitis, diabetic retinopathy and conjunctivitis, or any trauma caused by eye surgery or eye injury. The ophthalmologically acceptable antibiotic is preferably tobramycin which has been found not to interfere with the rate of diffusion of the NSAID. The combination of the NSAID and antibiotic is particularly effective in simultaneously preventing and/or eliminating infection while preventing and/or eliminating inflammation.

ABSTRACT OF THE DISCLOSURE

Stable, clear, antimicrobially effective, ophthalmic formulations are disclosed which provide an antimicrobially effective preservative. The formulations include an ophthalmologically effective amount of a drug, which is a -COOH group-containing non-steroidal anti-inflammatory drug (NSAID) in combination with an antibiotic drug, and a preservative system formed of a quaternary ammonium preservative and a nonionic polyoxyethylated octylphenol surfactant, all in an aqueous vehicle. The preservative system can be used with other formulations which require the preservative to be ophthamologically acceptable and antimicrobially effective. These formulations are useful for treating diseases and/or conditions that are either caused by, associated with or accompanied by inflammatory processes, including, among others, glaucoma, cystoid macular edema, uveitis, diabetic retinopathy and conjunctivitis, or any trauma caused by eye surgery or eye injury. The ophthalmologically acceptable antibiotic is preferably tobramycin which has been found not to interfere with the rate of diffusion of the NSAID. The combination of the NSAID and antibiotic is particularly effective in simultaneously preventing and/or eliminating infection while preventing and/or eliminating inflammation.

PRESERVATIVE SYSTEM FOR OPHTHALMIC FORMULATIONS

FIELD OF THE INVENTION

The present invention relates to improved ophthalmic formulations which use an improved preservative system comprising a quaternary ammonium preservative and a stabilizing amount of a nonionic polyoxyethylated octylphenol surfactant for ophthalmic formulations of carboxyl ("-COOH") group-containing non-steroidal anti-inflammatory drugs ("NSAIDs") and contain an opthalmologically acceptable antibiotic, preferably tobramycin. The invention also relates to methods of using these formulations for treating diseases and/or conditions that are either caused by, associated with or accompanied by inflammatory processes, including, among others, glaucoma, cystoid macular edema, uveitis, diabetic retinopathy and conjunctivitis, or any trauma caused by eye surgery or eye injury. In addition, the formulation can be used to treat bacterial infection.

BACKGROUND OF THE INVENTION

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

the general FDA requirements of being safe and effective. In that eyes are quite sensitive to pain, the formulation must be developed such that it causes little to no discomfort or stinging when administered. This feature is particularly important to insure user compliance and important in that such formulations are often administered in order to relieve pain or inflammation. The ophthalmic use of NSAID compounds was disclosed in U.S. Patent No. 4,454,151, where NSAID compounds (such as those described in U.S. Patents 4,089,969; 4,232,038; 4,087,539 and 4,097,579) were exemplified in formulation with NaH_2PO_4"H_2O, Na_2HPO_4"H_2O, NaCl, benzalkonium chloride ("BAC") and sterilized water. While the formulations described in the '151 patent were efficacious, a complex was found to form between the NSAID and the BAC.

Due to the formation of this complex, the formulations did not have the stability desired for shelf life in commercial applications. A reasonable minimum shelf life is at least about one year, representing sufficient time to package, ship, and store a formulation without having to replace expired stock too frequently.

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

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

In general, an ophthalmic formulation contains an active compound and various ophthalmologically acceptable excipients, in the form of a solution, an ointment, a suspension, etc. In order for an excipient to be ophthalmologically acceptable, it must be non-irritating to the eye in combination with other excipients and an active ingredient. The excipients must not prevent the active ingredient from penetrating the blood-aqueous barrier and/or diffusing through the various ocular substructures to the site where it is pharmacologically active. The excipients can interact with each other or the active drug. Accordingly, care in formulating is required in that so many materials may be used. These materials generally include a tonicifier, a preservative, a surfactant, a buffering system, a chelating agent, a viscosity agent as well as other stabilizing agents. Ophthalmic formulations must be sterile and must be preserved with an effective anti-microbial agent.

Organo-mercurials (e.g., thimerosal, phenylmercuric acetate and phenylmercuric nitrate) have been used extensively as the preservative in ophthalmic

solutions. These compounds, however, pose difficulties due to potential mercury toxicity as well as poor chemical stability. Benzalkonium chloride, a quaternary ammonium compound, has been widely used in ophthalmic solutions, and is considered to be the preservative of choice. However, BAC has typically been considered to be incompatible with anionic drugs (e.g., salicylates or nitrates, etc.) and can be inactivated by surfactants.

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

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

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

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

SUMMARY OF THE INVENTION

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

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

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

An advantage of the present invention is that it is useful in the treatment of diseases or conditions associated with or accompanied by inflammatory processes, including, among others, glaucoma, cystoid macular edema, uveitis, diabetic retinopathy and conjunctivitis, or any trauma caused by eye surgery or eye injury and eliminating infection.

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

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

DETAILED DESCRIPTION AND PREFERRED EMBODIMENTS

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

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

Definitions

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

As used herein, the term "q.s." means adding a

quantity sufficient to achieve a stated function, e.g., to bring a solution to the desired volume (i.e., 100%).

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

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

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

(iii) relieving the disease and/or condition, that is, causing the regression of clinical symptoms.

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

As used herein, the term "antimicrobially effective" refers to the stability of the formulation prior to administration and means ability to withstand the U.S. Pharmacopia antimicrobial challenge put by a panel of microbes.

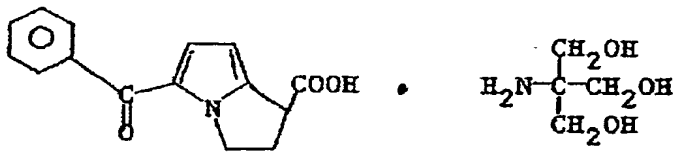
As used herein, the term "surfactant" means a nonionic surfactant, preferably ethoxylated octylphenol compounds as described below.

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

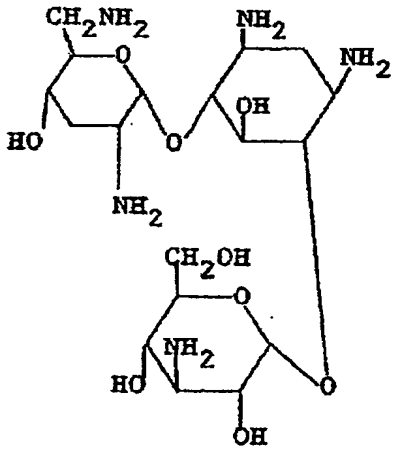
As used herein, the term "stabilizing" means keeping a formulation clear and antimicrobially effective for its minimum reasonable shelf life, e.g., at least one year.

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

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



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



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

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

Formulations

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

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

Ophthalmic solutions and suspensions typically contain an aqueous vehicle rather than an oily vehicle. Ophthalmic formulations must be sterile, and if intended for multiple dosing regimens, must be antimicrobially effective for their minimum reasonable shelf life, e.g., at least one year, and preferably two to three years or more. The ingredients used in the formulations of the present invention are typically commercially available or can be made by methods readily known to those skilled in the art.

Pharmaceutical ophthalmic formulations typically contain an effective amount, e.g., 0.001% to 10% wt/vol., preferably 0.002% to 5% wt/vol, most preferably 0.005% to 1% of an active ingredient (e.g., the NSAID of the present invention). The amount of active ingredient will vary with the particular formulation and the disease state for which it is intended. The total

concentration of solutes should be such that, if possible, the resulting solution is isotonic with the lacrimal fluid (though this is not absolutely necessary) and has a pH in the range of 6 to 8.

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

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

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

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

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

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

Ingredient	Amount
NSAID	0.50% wt/vol.;
Antibiotic	0.30% wt/vol.;
BAC (50% aq. soln.)	0.02% wt/vol.;
Octoxynol 40 (70% aq. soln.)	0.01% wt/vol.;
EDTA Na_2	0.10% wt/vol.;
NaCl/ boric acid/ Na borate	q.s. for isotonicity with lacrimal fluid;
1N NaOH or 1N HCl	q.s. to adjust pH to 7.4±0.4; and
Purified Water	q.s. to 100%.

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

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

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

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

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

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

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

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

Viscosity agents optionally useful in the formulations of the present invention include the cellulose derivatives such as hydroxypropylmethyl

cellulose, sodium carboxymethylcellulose, and hydroxyethylcellulose.

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

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

Ophthalmic formulations incorporating the preservative system of the invention are physically stable (i.e., remain clear) and functionally stable (i.e., remain antimicrobially effective) for at least the minimum reasonable shelf life of such products. The inclusion of an antibiotic in the formulation does not effect the rate of diffusion of the NSAID.

Preferred Formulations

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

The preferred preservative of the invention is benzalkonium chloride.

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

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

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

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

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

Ingredient	Amount
NSAID	0.50% wt/vol.
antibiotic	0.30% wt/vol.
BAC (50% aq. soln.)	0.02% wt/vol.
Octoxynol 40 (70% aq. soln.)	0.01% wt/vol.
EDTA Na_2	0.10% wt/vol.
(NaCl/boric acid/ Na borate)	q.s. for isotonicity with lacrimal fluid
1N NaOH or 1N HCl	q.s. to adjust pH to 7.4±0.4
Purified Water	q.s. to 100%

Most preferred is the ophthalmic solution according to the above formulations is wherein the NSAID is Ketorolac Tromethamine and when the antibiotic is present it is tobramycin.

Utility and Administration

This invention is directed to NSAID ophthalmic formulations and a method useful for treating ophthalmic diseases in mammals. These diseases are either caused by, associated with or accompanied by inflammatory

processes, including, among others, glaucoma, cystoid macular edema, uveitis, diabetic retinopathy and conjunctivitis, or any trauma caused by eye surgery or eye injury.

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

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

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

The dosage level will, of course, depend on the concentration of the drops, the condition of the subject and the individual magnitude of responses to treatment. However, typical dosage ranges might be about 2 to 10 drops of solution of active ingredient per day wherein the solution includes 0.5 wt/vol.% of Ketorolac trimethamine and 0.3 wt/vol.% of tobramycin.

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

Testing

Ophthalmic formulations such as the solutions of

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

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

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

EXAMPLES

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

EXAMPLE 1

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

Tromethamine and the antibiotic tobramycin.

Ingredient	Amount
ketorolac tromethamine	0.50% wt/vol.
tobramycin	0.30% wt/vol.
BAC (50% aq. soln.)	0.02% wt/vol.
Octoxynol 40 (70% aq. soln.)	0.01% wt/vol.
EDTA Na_2	0.10% wt/vol.
NaCl	0.18% wt/vol.
Boric Acid	0.9% wt/vol.
Na Borate	0.45% wt/vol.

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

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

EXAMPLE 2

This example illustrates the preparation of a general pharmaceutical formulation for ophthalmic

administration containing an NSAID and an antibiotic.

Ingredient	Amount
NSAID	0.50% wt/vol.
antibiotic	0.3% wt/vol.
BAC (50% aq. soln.)	0.01% wt/vol.
Octoxynol 40 (70% aq. soln.)	0.02% wt/vol.
EDTA Na_2	0.20% wt/vol.
NaCl	0.18% wt/vol.
Boric Acid	0.9% wt/vol.
Na Borate	0.45% wt/vol.

EXAMPLE 3

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

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

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

formulation of any of these examples.

EXAMPLE 4

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

Ingredient	Amount
Flurbiprofen Sodium	0.03% wt/vol.
BAC (50% aq. soln.)	0.02% wt/vol.
Octoxynol 40 (70% aq. soln.)	0.01% wt/vol.
EDTA Na_2	0.10% wt/vol.
NaCl	0.18% wt/vol.
Boric Acid	0.9% wt/vol.
Na Borate	0.45% wt/vol.

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

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

EXAMPLE 5

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

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

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

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

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

EXAMPLE 6

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

TABLE I

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

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

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

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

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

WHAT IS CLAIMED IS:

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

an ophthalmologically acceptable non-steroidal anti-inflammatory carboxyl group-containing drug in an effective amount for ophthalmic treatment;

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

a quaternary ammonium preservative;

a stabilizing amount of a nonionic polyoxyethylated octylphenol surfactant; and

an aqueous vehicle.

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

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

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

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

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

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

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

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

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

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

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

Claim 8, further comprising:

Chelating agent	0.01% to 1.0% wt/vol.;
Tonicifier	q.s. to achieve isotonicity with lacrimal fluid; and
1N NaOH or 1N HCl	q.s. to adjust pH to 7.4%0.4.

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

ketorolac tromethamine	0.50% wt/vol.;
Tobramycin	0.30% wt/vol.;
BAC (50% aq. soln.)	0.02% wt/vol.;
Octoxynol 40 (70% aq. soln.)	0.01% wt/vol.;
EDTA Na_2	0.10% wt/vol.;
NaCl	0.18% wt/vol.;
Boric Acid	0.9% wt/vol.
Na Borate	0.45% wt/vol.
1N NaOH or 1N HCl	q.s. to adjust pH to 7.4%0.4; and
Purified Water	q.s. to 100%.

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

vehicle for treating ophthalmic disease in a mammal suffering therewith.

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

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

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

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

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

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
21 February 2002 (21.02.2002)

PCT

(10) International Publication Number
WO 02/13804 A2

(51) International Patent Classification[7]: A61K 31/00

(21) International Application Number: PCT/US01/25318

(22) International Filing Date: 13 August 2001 (13.08.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/225,133 14 August 2000 (14.08.2000) US

(71) Applicant *(for all designated States except US)*: **ALCON UNIVERSAL LTD.** [CH/CH]; Bosch 69, P. O. Box 62, CH-6331 Hunenberg (CH).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **KAPIN, Michael, A.** [US/US]; 3602 Silkwood Trail, Arlington, TX 76016 (US). **BINGAMAN, David, P.** [US/US]; 875 Kickapoo Falls Road, Lipan, TX 76462 (US). **GAMACHE, Daniel, A.** [US/US]; 5610 Hunterwood Lane, Arlington, TX 76017 (US). **GRAFF, Gustav** [US/US]; 6500 County Road 809, Cleburne, TX 76031 (US). **YANNI, John, M.** [US/US]; 2821 Donnybrook Drive, Burleson, TX 76028 (US).

(74) Agents: **RYAN, Patrick, M.** et al.; R & D Counsel Q-148, 6201 South Freeway, Fort Worth, TX 76134-2099 (US).

(81) Designated States *(national)*: AU, BR, CA, CN, JP, KR, MX, PL, US, ZA.

(84) Designated States *(regional)*: European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR).

Published:
— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 02/13804 A2

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

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

METHOD OF TREATING ANGIOGENESIS-RELATED DISORDERS

FIELD OF THE INVENTION

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

BACKGROUND OF THE INVENTION

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

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

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

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

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

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

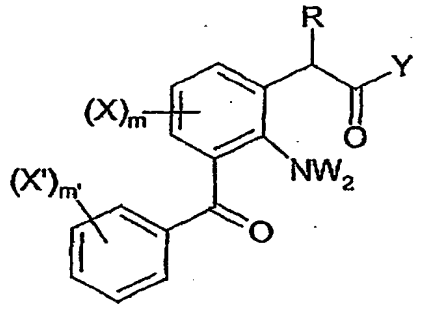
U.S. Patent No. 6,066,671 discloses the topical use of certain amide and ester derivatives of 3-benzoylphenylacetic acid, including nepafenac, for treating GLC1A glaucoma.

SUMMARY OF THE INVENTION

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

DETAILED DESCRIPTION OF THE INVENTION

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



(I)

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

Y = OR', NR"R';

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

n = 2-6;

n'= 1-6;

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

n^2 = 0-2;

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

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

R" = H, OH, OR';

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

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

m = 0-3;

m' = 0-5;

W = O, H.

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

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

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

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

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

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

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

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

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

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

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

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

Formulation 1

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

Formulation 2

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

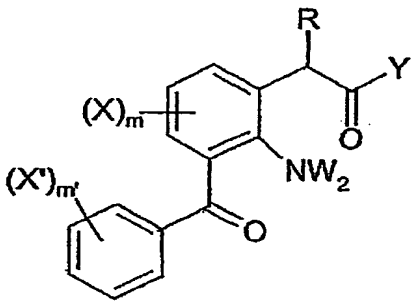
Formulation 3

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

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

We Claim:

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



wherein

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

Y = OR', NR"R';

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

n = 2-6;

n'= 1-6;

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

n^2 = 0-2;

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

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

R" = H, OH, OR';

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

R^4 = C_{1-6} (un)branched alkyl;
m = 0-3;
m' = 0-5; and
W = O, H.

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

3. The method of Claim 2 wherein the 3-benzoylphenylacetic acid or derivative is selected from the group consisting of 2-Amino-3-(4-fluorobenzoyl)-phenylacetamide; 2-Amino-3-benzoyl-phenylacetamide; and 2-Amino-3-(4-chlorobenzoyl)-phenylacetamide.

4. The method of Claim 1 wherein the angiogenesis-related disorder is an ophthalmic angiogenesis-related disorder.

5. The method of Claim 4 wherein the 3-benzoylphenylacetic acid or derivative is topically administered to the eye.

6. The method of Claim 5 wherein the therapeutically effective amount of 3-benzoylphenylacetic acid or derivative is from about 0.001 to about 4.0% (w/v).

7. The method of Claim 4 wherein the angiogenesis-related disorder is selected from the group consisting of exudative macular degeneration; proliferative diabetic retinopathy; ischemic retinopathy; retinopathy of prematurity; neovascular glaucoma; iritis rubeosis; corneal neovascularization; cyclitis; sickle cell retinopathy; and pterygium.

8. The method of Claim 1 wherein the 3-benzoylphenylacetic acid or derivative is administered orally, intravenously, in a subconjunctival injection or implant, in a sub-Tenon's injection or implant, in an intravitreal injection or implant, or in a surgical irrigating solution.

9. The method of Claim 1 wherein the angiogenesis-related disorder is selected from the group consisting of prostate cancer; lung cancer; breast cancer; bladder cancer; renal cancer; colon cancer; gastric cancer; pancreatic cancer; ovarian cancer; melanoma; hepatoma; sarcoma; and lymphoma.

AUSTRALIAN PATENT PUBLICATION

Application Number AU199514852B2
Patent Number AU707119B2

Title	Method for stabilizing pranoprofen and stable liquid preparation of pranoprofen
Classification(s)	A61K031/44
Application Number	AU199514852B2
Priority Data	JP 6-44184 (1994-03-15)
Filing Date	1995-03-15
Publication Date	1995-09-21
Publication Journal Date	1995-09-21
Accepted Journal Date	1999-07-01
Applicant(s)	Senju Pharmaceutical Co, Ltd
Inventor(s)	Koji Doi ; Hisako Sawa ; Yoshie Ozaki ; Yoshiyuki Kimura
Agent(s)	GRIFFITH HACK,GPO Box 4164,SYDNEY NSW 2001
Related Art	US 4525348 ; US 5032392 ; EP 0471084

AU9514852

(12) PATENT ABSTRACT (11) Document No. AU-A-14852/95
(19) AUSTRALIAN PATENT OFFICE

(54) Title
METHOD FOR STABILIZING PRANOPROFEN AND STABLE LIQUID PREPARATION OF PRANOPROFEN

International Patent Classification(s)
(51)[5] **A61K 031/44**

(21) Application No. : **14852/95** (22) Application Date : **15.03.95**

(30) Priority Data

(31) Number	(32) Date	(33) Country
6-44184	15.03.94	JP JAPAN

(43) Publication Date : **21.09.95**

(71) Applicant(s)
SENJU PHARMACEUTICAL CO, LTD

(72) Inventor(s)
KOJI DOI; HISAKO SAWA; YOSHIE OZAKI; YOSHIYUKI KIMURA

(74) Attorney or Agent
GRIFFITH HACK & CO., GPO Box 4164, SYDNEY NSW 2001

(57)

A method for stabilizing pranoprofen, comprising placing an aqueous solution of pranoprofen in coexistence with an antioxidant, or placing an aqueous solution of pranoprofen under the conditions of limited supply of oxygen, and a stable aqueous preparation of pranoprofen, comprising pranoprofen and an antioxidant. According to the present invention, the decomposition of pranoprofen in an aqueous solution of pranoprofen is remarkably suppressed. In particular, pranoprofen becomes stable to light, thus permitting long-term preservation of an aqueous solution, specifically a liquid preparation, of pranoprofen.

ABSTRACT OF THE DISCLOSURE

A method for stabilizing pranoprofen, comprising placing an aqueous solution of pranoprofen in coexistence with an antioxidant, or placing an aqueous solution of pranoprofen under the conditions of limited supply of oxygen, and a stable aqueous preparation of pranoprofen, comprising pranoprofen and an antioxidant. According to the present invention, the decomposition of pranoprofen in an aqueous solution of pranoprofen is remarkably suppressed. In particular, pranoprofen becomes stable to light, thus permitting long-term preservation of an aqueous solution, specifically a liquid preparation, of pranoprofen.

P/00/011
Regulation 3.2

AUSTRALIA

Patents Act 1990

ORIGINAL

COMPLETE SPECIFICATION

STANDARD PATENT

Invention Title: METHOD FOR STABILIZING PRANOPROFEN AND STABLE LIQUID PREPARATION OF PRANOPROFEN

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

GH&CO REF: P21942-L:ADK:RK

SPECIFICATION

METHOD FOR STABILIZING PRANOPROFEN AND STABLE LIQUID PREPARATION OF PRANOPROFEN

FIELD OF THE INVENTION

The present invention relates to a method for stabilizing pranoprofen having anti-inflammatory activity, in an aqueous solution of pranoprofen, and to a liquid preparation comprising, as an active ingredient, pranoprofen which is stabilized by adding an antioxidant.

BACKGROUND OF THE INVENTION

Pranoprofen having a chemical name of α-methyl-5H-[1]benzopyrano[2,3-b]pyridine-7-acetic acid exhibits prominent anti-inflammatory action, analgesic action and antipyretic action. It is a non-steroidal anti-inflammatory drug having a wider safety margin, and is commercially available by the product name of Niflan (trademark). The properties and production method thereof are described in United States Patent No. 3931295.

There has also been proposed an eye drop containing pranoprofen as an anti-inflammatory active ingredient and boric acid as an isotonizing agent, as being useful for, in particular, herpesvirus eye diseases (US Patent No. 4,607,038).

However, pranoprofen is unstable in an aqueous solution state (particularly to light) and is gradually decomposed during long-term preservations.

It is therefore an object of at least a preferred

embodiment of the present invention to provide a method for stabilizing pranoprofen in an aqueous solution state.

Another object of at least a preferred embodiment of the present invention is to provide an aqueous solution of pranoprofen, wherein decomposition of pranoprofen is suppressed.

According to the present invention, it has now been found that decomposition of pranoprofen can be markedly suppressed by placing an aqueous solution of pranoprofen in coexistence with an antioxidant, or placing an aqueous solution of pranoprofen under the conditions of limited supply of oxygen.

That is, the present invention and preferable modes thereof are as follows.

(1) A method for stabilizing pranoprofen, comprising placing an aqueous solution of pranoprofen in coexistence with an antioxidant.

(2) A method for stabilizing pranoprofen according to (1), comprising adding an antioxidant to an aqueous solution of pranoprofen.

(3) A method for stabilizing pranoprofen according to (2), wherein the weight ratio of the antioxidant to pranoprofen is 0.0002-5.0:1.

(4) A method for stabilizing pranoprofen according to (1), comprising sealing an aqueous solution of pranoprofen in a container formed from a mixture comprising a material for the container and an antioxidant.

(5) A method for stabilizing pranoprofen according to (4),

wherein the weight ratio of the antioxidant to the material is 0.0001-0.005:1.

(6) A method for stabilizing pranoprofen according to (4), wherein the container is made of polypropylene.

(7) A method for stabilizing pranoprofen according to (2), wherein the antioxidant is at least one compound selected from the group consisting of alkylphenols, benzopyran derivatives, sodium thiosulfate and amino acids.

(8) A method for stabilizing pranoprofen according to (7), wherein the alkylphenol is at least one compound selected from the group consisting of dibutylhydroxytoluene and butylhydroxyanisole.

(9) A method for stabilizing pranoprofen according to (7), wherein the benzopyran derivative is at least one member selected from the group consisting of L-ascorbic acid 2-[3,4-dihydro-2,5,7,8-tetramethyl-2-(4,8,12-trimethyltridecyl)-2H-1-benzopyran-6-yl-hydrogen phosphate] and salts thereof.

(10) A method for stabilizing pranoprofen according to (7), wherein the amino acid is at least one member selected from the group consisting of methionine, tryptophan and histidine.

(11) A method for stabilizing pranoprofen according to any one of (4)-(6), wherein the antioxidant is at least one alkylphenol.

(12) A method for stabilizing pranoprofen according to (11), wherein the alkylphenol is at least one member selected from the group consisting of dibutylhydroxytoluene and

butylhydroxyanisole.

(13) A method for stabilizing pranoprofen, comprising placing an aqueous solution of pranoprofen under the conditions of limited supply of oxygen.

(14) A method for stabilizing pranoprofen according to (13), comprising sealing a container, in which an aqueous solution of pranoprofen has been sealed, in a container or enclosing the container with a sheet, together with a deoxygenating agent.

(15) A method for stabilizing pranoprofen according to (13), comprising sealing an aqueous solution of pranoprofen in a container having a low oxygen permeability or enclosing the solution with a sheet having a low oxygen permeability.

(16) A stabilizing method according to (1), wherein the aqueous solution of pranoprofen is an eye drop or a collunarium.

(17) A stabilizing method according to (13), wherein the aqueous solution of pranoprofen is an eye drop or a collunarium.

(18) A stable liquid preparation of pranoprofen, comprising pranoprofen and an antioxidant.

(19) The liquid preparation of (18), wherein the antioxidant is at least one compound selected from the group consisting of alkylphenols, benzopyran derivatives, sodium thiosulfate and amino acids.

(20) The liquid preparation of (19), wherein the alkylphenol is at least one member selected from the group consisting of dibutylhydroxytoluene and butylhydroxyanisole.

(21) The liquid preparation of (19), wherein the benzopyran

derivative is at least one compound selected from the group consisting of L-ascorbic acid 2-[3,4-dihydro-2,5,7,8-tetramethyl-2-(4,8,12-trimethyltridecyl)-2H-1-benzopyran-6-yl-hydrogen phosphate] and salts thereof.

(22) The liquid preparation of (19), wherein the amino acid is at least one member selected from the group consisting of methionine, tryptophan and histidine.

(23) The liquid preparation of (18), wherein the weight ratio of the antioxidant to pranoprofen is 0.0002-5.0:1.

(24) The liquid preparation of (18), which is an eye drop.

(25) The liquid preparation of (18), which is a collunarium.

The first mode of the stabilizing method of the present invention is placing an aqueous solution of pranoprofen in coexistence with an antioxidant, which is realized by, for example, (i) adding an antioxidant to an aqueous solution of pranoprofen (Mode I) or (ii) sealing an aqueous solution of pranoprofen in a container formed from a mixture comprising a material for the container and an antioxidant (Mode II). The Modes I and II may be used in combination.

The antioxidant to be used in Mode I includes, for example, alkylphenols, benzopyran derivatives, sodium thiosulfate and amino acids.

Examples of alkylphenol include dibutylhydroxytoluene (BHT), butylhydroxyanisole (BHA), n-propyl gallate and catechol, with preference given to BHT and BHA.

Examples of benzopyran derivative include tocopherol, tocol, L-ascorbic acid 2-[3,4-dihydro-2,5,7,8-tetramethyl-2-(4,8,12-trimethyltridecyl)-2H-1-benzopyran-6-yl-hydrogen phosphate] and salts thereof, with preference given to L-ascorbic acid 2-[3,4-dihydro-2,5,7,8-tetramethyl-2-(4,8,12-trimethyltridecyl)-2H-1-benzopyran-6-yl-hydrogen phosphate] potassium salt (EPC-K_1).

Amino acid is, for example, methionine, tryptophan or histidine, with preference given to methionine and tryptophan.

When an antioxidant is added to an aqueous solution of pranoprofen according to Mode I, the weight ratio of the antioxidant to pranoprofen is generally 0.0002-5.0:1, preferably 0.002-2.5:1.

When an aqueous solution of pranoprofen is sealed in a container formed from a mixture comprising a material for the container and an antioxidant, according to Mode II, the material for the container is exemplified by those generally used for plastic containers, such as polyolefin [e.g. polyethylene (PE) and polypropylene (PP)], with preference given to PP.

The mixture for the container comprises a material for the container and an antioxidant. The weight ratio of the antioxidant to the material is, for example, 0.0001-0.005:1, preferably 0.0005-0.005:1.

In the Mode II, the antioxidant to be used is, for example, a phenol such as alkylphenol, alkyldiphenol or thiobisalkylphenol.

Examples of alkylphenol include dibutylhydroxytoluene

(BHT), butylhydroxyanisole (BHA), n-propyl gallate, stearyl ß-(3,5-di-t-butyl-4-hydroxyphenyl)propionate, tetrakis[3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionyloxymethyl]methane, 1,3,5-tris(3,5-di-tert-butyl-4-hydroxybenzyl)-1H,2H,3H-triazine-2,4,6-trione, 1,3,5-tris[(3,5-di-tert-butyl-4-hydroxybenzyl)-2,4,6-trimethyl]benzene and 3,9-bis[2-(3-(3-tert-butyl-4-hydroxy-5-methylphenyl)propionyloxy)-1,1-dimethylethyl]-2,4,8,10-tetraoxaspiro[5.5]undecane, with preference given to BHT and BHA.

Examples of alkyldiphenol include 2,2'-methylenebis(4-methyl-6-tert-butylphenol), 4,4'-butylidenebis(2-tert-butyl-5-methylphenol) and 2-tert-butyl-6-(3-tert-butyl-2-hydroxy-5-methylbenzyl)-4-methylphenyl acrylate.

Examples of thiobisalkylphenol include 4,4'-thiobis(2-tert-butyl-5-methylphenol).

The second mode of the stabilizing method of the present invention is placing an aqueous solution of pranoprofen under the conditions of limited oxygen supply. For example, a container containing an aqueous solution of pranoprofen sealed therein is sealed in another container or enclosed with a sheet in coexistence with a deoxygenating agent (Mode III), or an aqueous solution of pranoprofen is sealed in a container having a low oxygen permeability, or enclosed with a sheet having a low oxygen permeability (Mode IV).

In the Mode III, the container for sealing an aqueous solution of pranoprofen is subject to no particular limitation

as long as it can seal an aqueous solution of pranoprofen, and is preferably exemplified by a container formed from a mixture comprising a material for the container and an antioxidant, such as those exemplified for the above-mentioned Mode II, and a container having a low oxygen permeability to be mentioned below.

The deoxygenating agent to be used in Mode III is exemplified by iron powder, iron oxide, ascorbic acid and catechol, with preference given to iron oxide. The deoxygenating agent is preferably packed in a bag etc. made of an oxygen-permeable material and put to use.

The container and the sheet to enclose a container, in which an aqueous solution of pranoprofen has been sealed, together with a deoxygenating agent according to Mode III, are not subject to any particular limitation as long as they can enclose both the container, in which an aqueous solution of pranoprofen has been sealed, and a deoxygenating agent in such a manner that the outside air is shut off from them. Examples of the container include plastic containers and glass containers, and examples of the sheet include plastic sheets and aluminum sheets. The materials for such containers and sheets may be added with an antioxidant, as exemplified in the above-mentioned Mode II, or may have a low oxygen permeability as discussed below. Also, an antioxidant may be added to an aqueous solution of pranoprofen in Mode III.

The container and the sheet having low oxygen permeability, which are to be used in Mode IV, are preferably made from a

material having an oxygen permeability of not more than 120 cc/m² · 24 hr · atm [20℃ · 90% relative humidity (RH), thickness of material 25 μm], preferably not more than 70 cc/m² · 24 hr · atm (20℃ · 90% RH, thickness of material 25 μm), such as those made from acrylonitrile resins [e.g. acrylonitrile styrene (AS) and acrylonitrile butadiene styrene (ABS)] and polyethy ene terephthalate (PET), with particular preference given to those made from PET.

The solvent to be used to prepare a liquid preparation and an aqueous solution of pranoprofen of the present invention is exemplified by sterile purified water, in particular, distilled water for injection. The concentration of the active ingredient pranoprofen is generally 0.01-2.0 w/v%, preferably 0.05-1.0 w/v%, which is increased or decreased as appropriate according to the object of use.

The antioxidant to be used for the liquid preparation of pranoprofen of the present invention is exemplified by those mentioned for Mode I.

The liquid preparation of the present invention may further contain various additives on demand, such as buffers, isotonizing agents, solubilizing agents, preservatives, thickeners, chelating agents, pH adjusting agents and aromatic agents.

Examples of buffer include phosphate buffer (e.g. sodium dihydrogenphosphate-disodium hydrogenphosphate and potassium dihydrogenphosphate-potassium hydroxide), borate buffer (e.g.

boric acid-sodium tetraborate), citrate buffer (e.g. sodium citrate-sodium hydroxide), tartrate buffer (e.g. tartaric acid-sodium tartrate), acetate buffer (e.g. acetic acid-sodium acetate), carbonate buffer (e.g. sodium carbonate-citric acid and sodium carbonate-boric acid) and amino acid (e.g. sodium glutamate and ε-aminocaproic acid).

When the liquid preparation of pranoprofen is used as an eye drop, it is preferable that borate buffer, acetate buffer or carbonate buffer be used to decrease irritation.

Examples of isotonizing agent include saccharides such as sorbitol, glucose and mannitol, polyhydric alcohols such as glycerol and propylene glycol, salts such as sodium chloride and sodium tetraborate, and boric acid.

Examples of solubilizing agent include non-ionic surfactants such as polyoxyethylenesorbitan monooleate (polysorbate 80), polyoxyethylenemonostearate, polyethylene glycol and polyoxyethylene hydrogenated castor oil.

Examples of preservative include quaternary ammonium salts such as benzalkonium chloride, benzethonium chloride and cetylpyridinium chloride, p-hydroxybenzoates such as methyl p-hydroxybenzoate, ethyl p-hydroxybenzoate, propyl p-hydroxybenzoate and butyl p-hydroxybenzoate, benzyl alcohol, phenetyl alcohol, sorbic acid and salts thereof, thimerosal, chlorobutanol and sodium dehydroacetate.

Examples of thickener include polyvinylpyrrolidone, hydroxyethylcellulose, hydroxypropylcellulose, methylcellulose,

hydroxypropylmethylcellulose, carboxymethylcellulose and salts thereof.

Examples of chelating agent include disodium edetate and citric acid.

Examples of pH-adjusting agent include hydrochloric acid, citric acid, phosphoric acid, acetic acid, tartaric acid, sodium hydroxide, potassium hydroxide, sodium carbonate and sodium hydrogencarbonate.

Examples of aromatic agent include 1-menthol, borneol, camphor (e.g. dl-camphor) and eucalyptus oil.

The liquid preparation of the present invention is used as an eye drop, collunarium and the like. When used as an eye drop, its pH is generally adjusted to about 6.0-8.5, preferably about 7.0-8.0, and when used as a collunarium, its pH is generally adjusted to about 6.0-8.5, preferably about 7.0-8.0.

While the method for producing the liquid preparation of the present invention varies depending on the kind of liquid preparation, a known method for each liquid preparation can be used.

The dose of the liquid preparation of the present invention, when used, for example, as an eye drop, is an amount sufficient to effectively resolve ophthalmic inflammation, and varies depending on symptoms and the kind of inflammation. The dose is generally 5.0-1,000 μg/administration, preferably 25-500 μg/administration, which is administered 2 to 5 times a day as appropriate.

The present invention is described in more detail in the following by referring to Experimental Examples and Examples.

Experimental Example 1 [Stability test - No. 1]

A solution of 0.1 w/v% pranoprofen [boric acid, 1.6 w/v%; sodium tetraborate, appropriate amount; disodium edetate, 0.01 w/v%; benzalkonium chloride, 0.005 w/v%; polysorbate 80, 0.1 w/v%; sterile purified water, appropriate amount] was filled in 5 ml polypropylene containers manufactured by adding BHT to 0.05, 0.1 or 0.5 w/v% [oxygen permeability of 25 μm thick test sample, 3,800 cc/m² · 24 hr · atm (20℃ · 90% RH); Gas Permeation Test Method of Plastic Film and Sheet of Japanese Industrial Standards, the equal pressure method [Japanese Standards Association, JIS Handbook, p 400, Tokyo (1991)]] and 15 ml polyethylene terephthalate containers [oxygen permeability of 25 μm thick test samples, 63 cc/m² · 24 hr · atm (20℃ · 90% RH); Gas Permeation Test Method of Plastic Film and Sheet of Japanese Industrial Standards, the equal pressure method [Japanese Standards Association, JIS Handbook, p 400, Tokyo (1991)]], and left standing in the dark at room temperature for 36 months. The residual content of pranoprofen in the containers was determined with time by high performance liquid chromatography. The results are shown in Table 1.

Table 1

Container	Residual content of pranoprofen (%)					
	On preparation	3 months	6 months	12 months	24 months	36 months
PP (control)	100.0	95.6	93.9	-	81.9	78.5
PP-05	100.0	100.4	99.3	99.0	98.5	100.2
PP-01	100.0	100.4	98.3	98.1	95.4	96.0
PP-005	100.0	100.4	98.3	97.0	93.2	93.3
PET	100.0	99.5	101.0	100.3	100.8	99.4

PP : polypropylene container without BHT
oxygen permeability, 3800 cc/m² · 24 hr · atm
(20℃ · 90% RH, 25 μm)

PP-05 : polypropylene container containing 0.5% BHT

PP-01 : polypropylene container containing 0.1% BHT

PP-005: polypropylene container containing 0.05% BHT

PET : polyethylene terephthalate container without BHT
oxygen permeability, 63 cc/m² · 24 hr · atm
(20℃ · 90% RH, 25 μm)

As is evident from Table 1, superior suppression of decomposition of pranoprofen was achieved by preserving pranoprofen in the containers (PP) formed from a mixture containing BHT and in the container (PET) having a low oxygen permeability.

Experimental Example 2 [Stability test - No. 2]

BHT or sodium thiosulfate was added to a basic formulation solution [pranoprofen, 0.1 w/v%; boric acid, 1.6 w/v%; sodium tetraborate, appropriate amount; disodium edetate, 0.01 w/v%; benzalkonium chloride, 0.005 w/v%; polysorbate 80, 0.1 w/v%; sterile purified water, appropriate amount], and the mixture was filled in 5 ml polypropylene containers. The

containers were left standing in the dark at room temperature for 39 months. The residual content of pranoprofen in the containers was determined by high performance liquid chromatography. The results are shown in Table 2.

Table 2

Compound added	Concentration (%)	Residual content of pranoprofen (%)	
		On preparation	after 39 months
Control (not added)	0	100.0	77.0
BHT	0.0004	100.0	99.6
〃	0.0001	100.0	94.7
sodium thiosulfate	0.1	100.0	93.0

As is evident from Table 2, superior suppression of decomposition of pranoprofen was achieved by the addition of respective antioxidants.

Experimental Example 3 [Stability test - No. 3]

BHT, BHA, L-ascorbic acid 2-[3,4-dihydro-2,5,7,8-tetramethyl-2-(4,8,12-trimethyltridecyl)-2H-1-benzopyran-6-yl-hydrogen phosphate] potassium salt (EPC-K_1), methionine, tryptophan or histidine was added to a basic formulation solution [pranoprofen, 0.05 w/v%; boric acid, 1.6 w/v%; sodium tetraborate, appropriate amount; disodium edetate, 0.01 w/v%; benzalkonium chloride, 0.005 w/v%; polysorbate 80, 0.1 w/v%; sterile purified water, appropriate amount], and the mixture was filled in colorless 15 ml polyethylene terephthalate containers. The containers were left standing under a fluorescent lamp (20 W). When the total irradiation reached

100,000 lux · hr, the residual content of pranoprofen in the containers was determined by high performance liquid chromatography. The results are shown in Table 3.

Table 3

Compound added	Concentration (%)	Residual content of pranoprofen (%)	
		On preparation	after irradiation of 100,000 lux · hr
Control (not added)	0	100.0	52.5
BHT	0.005	100.0	98.0
〃	0.002	100.0	96.6
〃	0.0002	100.0	70.8
BHA	0.002	100.0	92.8
EPC-K_1	0.05	100.0	79.1
〃	0.01	100.0	70.5
〃	0.001	100.0	68.2
methionine	0.24	100.0	95.2
tryptophan	0.06	100.0	96.9
histidine	0.13	100.0	75.9

As is evident from Table 3, the decomposition of pranoprofen caused by the exposure to the light was markedly suppressed by the addition of respective antioxidants.

Experimental Example 4 [Stability test - No. 4]

A solution of 0.1 w/v% pranoprofen [boric acid, 1.6 w/v%; sodium tetraborate, appropriate amount; disodium edetate, 0.01 w/v%; benzalkonium chloride, 0.005 w/v%; polysorbate 80, 0.1 w/v%; sterile purified water, appropriate amount] was filled in 5 ml polypropylene containers and the containers were tightly sealed. The containers were enclosed together with iron oxide (Ageless Z-30, manufactured by Mitsubishi Gas Chemical Company, Inc.) as a deoxygenating agent, with the use of a multi-layer

film of polypropylene/poly(vinyl alcohol)/polyethylene and left standing at room temperature for 30 months. The residual content of pranoprofen in the containers was determined with time by high performance liquid chromatography. The results are shown in Table 4.

Table 4

Enclosing	Residual content of pranoprofen (%)				
	On preparation	2 months	6 months	9 months	30 months
Unenclosed	100.0	95.1	89.4	92.0	80.3
Film-enclosed (deoxygenator)	100.0	98.1	97.6	97.2	101.0
Film-enclosed (N_2 substitution)	100.0	95.0	93.4	89.5	88.5

Containers used: polypropylene containers without BHT

Film: multi-layer film of polypropylene/poly(vinyl alcohol)/polyethylene

deoxygenating agent: iron oxide (Ageless Z-30, manufactured by Mitsubishi Gas Chemical Company, Inc.)

As is evident from Table 4, marked suppression of decomposition of pranoprofen was achieved by sealing a container, in which an aqueous solution of pranoprofen had been sealed, together with a deoxygenating agent.

Example 1 [Eye drop]

(1) Pranoprofen	0.2	g
(2) Disodium hydrogenphosphate	0.5	g
(3) Sodium dihydrogenphosphate	0.1	g
(4) Polyoxyethylene hydrogenated castor oil 60	0.1	g
(5) Poly(vinyl alcohol)	0.2	g

(6)	Sodium chloride	0.8 g
(7)	Benzethonium chloride	0.007 g
(8)	BHT	0.01 g
(9)	Sodium hydroxide	appropriate amount
(10)	Sterile purified water	appropriate amount
	Total	100 ml

(5) was added to about 70 ml of (10) and the mixture was stirred with heating to about 70℃ for dissolution. (4) and (8) were added to this solution and the mixture was admixed until it became a uniform dispersion. The mixture was cooled to room temperature. (1), (2), (3), (6) and (7) were dissolved in this solution and pH was adjusted to 7.2 with (9). (10) was added to make the total amount 100 ml and the mixture was filled in a 5 ml PE container for an eye drop.

Example 2 [Eye drop]

(1)	Pranoprofen	0.4 g
(2)	Sodium chloride	0.5 g
(3)	Polysorbate 80	0.15 g
(4)	Polyethylene glycol	0.5 g
(5)	Citric acid	0.2 g
(6)	Benzalkonium chloride	0.009 g
(7)	Sodium thiosulfate	0.01 g
(8)	Sodium carbonate	appropriate amount
(9)	Sterile purified water	appropriate amount
	Total	100 ml

(1), (2), (3), (4), (5), (6) and (7) were dissolved in

about 70 ml of (9) and pH was adjusted to 8.0 with (8). (9) was added to make the total amount 100 ml and the mixture was filled in a 5 ml PP container for an eye drop.

Example 3 [Eye drop]

(1) Pranoprofen	0.1 g
(2) Potassium dihydrogenphosphate	0.3 g
(3) Conc. glycerol	2.6 g
(4) Potassium hydroxide	appropriate amount
(5) Disodium edetate	0.01 g
(6) EPC-K_1	0.05 g
(7) Methyl p-hydroxybenzoate	0.026 g
(8) Propyl p-hydroxybenzoate	0.014 g
(9) Sterile purified water	appropriate amount
Total	100 ml

About 80 ml of (9) was heated to about 90℃ and (7) and (8) were dissolved. The mixture was cooled to room temperature. An appropriate amount of (4) was dissolved and then, (1), (2), (3), (5) and (6) were dissolved. Its pH was adjusted to 6.5 with (4). (9) was added to make the total amount 100 ml and the mixture was filled in a 10 ml polycarbonate container for an eye drop.

Example 4 [Eye drop]

(1) Pranoprofen	0.1 g
(2) Boric acid	1.6 g
(3) Sodium tetraborate	appropriate amount
(4) Disodium edetate	0.01 g

(5) Polysorbate 80	0.15 g
(6) Benzalkonium chloride	0.007 g
(7) Sterile purified water	appropriate amount
Total	100 ml

(1), (2), (3), (4), (5) and (6) were dissolved in about 80 ml of (7), and pH was adjusted to 7.0 with (3). (7) was added to make the total amount 100 ml and the mixture was filled in a 5 ml PP container for an eye drop, which comprised 0.5% BHT.

Example 5 [Eye drop]

(1) Pranoprofen	0.1 g
(2) Boric acid	1.6 g
(3) Sodium tetraborate	appropriate amount
(4) Disodium edetate	0.01 g
(5) Polysorbate 80	0.15 g
(6) Benzalkonium chloride	0.007 g
(7) Sterile purified water	appropriate amount
Total	100 ml

(1), (2), (3), (4), (5) and (6) were dissolved in about 80 ml of (7), and pH was adjusted to 7.0 with (3). (7) was added to make the total amount 100 ml and the mixture was filled in a 5 ml PP container for an eye drop. The container and iron oxide (Ageless Z-30; manufactured by Mitsubishi Gas Chemical Company, Inc.) were enclosed with a multi-layer film of polypropylene/poly(vinyl alcohol)/polyethylene.

Example 6 [Eye drop]

(1) Pranoprofen	0.05 g

(2) Boric acid	1.6 g
(3) Sodium tetraborate	appropriate amount
(4) Disodium edetate	0.01 g
(5) Benzalkonium chloride	0.005 g
(6) 1-menthol	0.002 g
(7) dl-camphor	0.0005 g
(8) Polysorbate 80	0.1 g
(9) Sterile purified water	appropriate amount
Total	100 ml

(1), (2), (3), (4) and (5) were dissolved in about 70 ml of (9). (6), (7) and (8) were admixed and uniformly dispersed in about 20 ml of (9) heated to about 60℃. This dispersion was added to the above-mentioned solution. The pH of the mixture was adjusted to 7.5 with (3) and (9) was added to make the total amount 100 ml. The mixture was filled in a 15 ml PET container for an eye drop and enclosed to avoid light.

Example 7 [Collunarium]

(1) Pranoprofen	0.4 g
(2) Sodium citrate	0.2 g
(3) Polysorbate 80	0.1 g
(4) Glycerol	2.6 g
(5) Benzethonium chloride	0.007 g
(6) Methionine	0.24 g
(7) Sodium hydroxide	appropriate amount
(8) Sterile purified water	appropriate amount
Total	100 ml

(1), (2), (3), (4), (5) and (6) were dissolved in about 70

ml of (8), and pH was adjusted to 7.5 with (7). (8) was added to make the total amount 100 ml and the mixture was filled in a 5 ml PP container for a collunarium.

Example 8 [Collunarium]

(1) Pranoprofen	1.0	g
(2) Boric acid	1.2	g
(3) Sodium tetraborate	0.8	g
(4) Disodium edetate	0.01	g
(5) Polysorbate 80	0.15	g
(6) Benzalkonium chloride	0.007	g
(7) Sodium hydroxide	appropriate amount	
(8) Sterile purified water	appropriate amount	
Total	100 ml	

(1), (2), (3), (4), (5) and (6) were dissolved in about 80 ml of (8), and pH was adjusted to 7.0 with (7). (8) was added to make the total amount 100 ml and the mixture was filled in a 8 ml PE container for a collunarium. The container and iron oxide (Ageless Z-30; manufactured by Mitsubishi Gas Chemical Company, Inc.) were enclosed with a multi-layer film of polypropylene/poly(vinyl alcohol)/polyethylene.

According to the present invention, the decomposition of the active ingredient pranoprofen is remarkably suppressed. In particular, pranoprofen becomes stable to light, thus permitting long-term preservation of an aqueous solution (preparation) of pranoprofen.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A method for stabilizing pranoprofen, comprising adding an antioxidant to an aqueous solution of pranoprofen in the presence of a non-ionic surfactant, wherein the antioxidant is at least one compound selected from the group consisting of alkylphenols, benzopyran derivatives, sodium thiosulfate and amino acids.

2. The method for stabilizing pranoprofen according to Claim 1, wherein the weight ratio of the antioxidant to pranoprofen is 0.0002-5.0:1.

3. The method for stabilizing pranoprofen according to Claim 1, wherein the alkylphenol is at least one compound selected from the group consisting of dibutylhydroxytoluene and butylhydroxyanisole.

4. The method for stabilizing pranoprofen according to Claim 1, wherein the benzopyran derivative is at least one compound selected from the group consisting of L-ascorbic acid 2-[3,4-dihydro-2,5,7,8-tetramethyl-2-(4,8,12-trimethyltridecyl)-2H-1-benzopyran-6-yl-hydrogen phosphate] and salts thereof.

5. The method for stabilizing pranoprofen according to Claim 1, wherein the amino acid is at least one compound selected from the group consisting of methionin, tryptophan and histidine.

6. The stabilizing method according to Claim 1, wherein the aqueous solution of pranoprofen is an eye drop or collunarium.

7. A stable liquid preparation of pranoprofen, comprising pranoprofen and an antioxidant in the presence of a non-ionic surfactant, wherein the antioxidant is at least one compound selected from the group consisting of alkylphenols, benzopyran derivatives, sodium thiosulfate and amino acids.

8. The liquid preparation of Claim 7, wherein the alkylphenol is at least one compound selected from the group consisting of dibutylhydroxytoluene and butylhydroxyanisole.

9. The liquid preparation of Claim 7, wherein the benzopyran derivative is at least one compound selected from the group consisting of L-ascorbic acid 2-[3,4-dihydro-2,5,7,8-tetramethyl-2-(4,8,12-trimethyltridecyl)-2H-1-benzopyran-6-yl-hydrogen phosphate] and salts thereof.

10. The liquid preparation of Claim 7, wherein the amino acid is at least one compound selected from the group consisting of methionin, tryptophan and histidine.

11. The liquid preparation of Claim 7, wherein the weight ratio of the antioxidant to pranoprofen is 0.0002-5.0:1.

12. The liquid preparation of Claim 7, which is an eye drop.

13. The liquid preparation of Claim 7, which is a collunarium.

14. The method for stabilising pranoprofen of claim 1, wherein the non-ionic surfactant is at least one member selected from the group consisting of polyoxyethylenesorbitan monooleate, polyoxyethylene monostearate, polyethylene glycol and polyoxyethylene hydrogenated castor oil.

15. The liquid preparation of pranoprofen of claim 7, wherein the non-ionic surfactant is at least one member selected from the group consisting of polyoxyethylenesorbitan monooleate, polyoxyethylene monostearate, polyethylene glycol and polyoxyethylene hydrogenated castor oil.

16. A stable liquid preparation of pranoprofen according to claim 7 substantially as herein described with reference to any one of the Examples.

Dated this 3rd day of May 1999
SENJU PHARMACEUTICAL CO., LTD.
By their Patent Attorneys
GRIFFITH HACK

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of	:	**Confirmation No. 1756**
Shirou SAWA et al.	:	Attorney Docket No. 2005_0232A
Serial No. 10/525,006	:	Group Art Unit 1614
Filed March 28, 2005	:	Examiner Timothy P. Thomas
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 July 18, 2007, the time for responding thereto being extended for three months in accordance with a petition for extension submitted concurrently herewith, please amend the above-identified application as follows:

Amendments to the Claims

1-18. (Cancelled)

19. (Currently amended) An aqueous liquid preparation comprising at least the following two components, the first component comprising 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof, and the second component comprising an alkyl aryl polyether alcohol type polymer or a polyethylene glycol fatty acid ester, wherein said liquid preparation is in the form of an eye drop.

20. (Previously presented) The aqueous liquid preparation according to claim 19, wherein the alkyl aryl polyether alcohol type polymer is tyloxapol;

wherein the concentration of the tyloxapol is selected from a range of about 0.01 w/v % to about 0.5 w/v %; and

wherein the concentration of the 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof is selected from a range of about 0.01 to about 0.5 w/v %.

21. (Previously presented) The aqueous liquid preparation according to claim 20, wherein the pharmacologically acceptable salt of 2-amino-3-(4-bromobenzoyl)phenylacetic acid is a sodium salt.

22. (Previously presented) The aqueous liquid preparation according to claim 21, wherein the concentration of the 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt is selected from a range of about 0.05 to about 0.2 w/v %.

23. (Previously presented) The aqueous liquid preparation according to claim 22, wherein the concentration of the tyloxapol is selected from a range of about 0.01 w/v % to about 0.3 w/v %.

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

25. (Previously presented) The aqueous liquid preparation according to claim 24, wherein the concentration of the tyloxapol is about 0.02 w/v %.

26. (Previously presented) The aqueous liquid preparation according to claim 25, wherein the formulation further includes one or more additives selected from the group consisting of a preservative, buffer, thickener, stabilizer, chelating agent, and pH controlling agent.

27. (Previously presented) The aqueous liquid preparation according to claim 26, wherein said preservative is benzalkonium chloride; wherein said buffer is boric acid and/or sodium borate; wherein said thickener is polyvinylpyrrolidone; wherein said stabilizer is sodium sulfite; wherein said chelating agent is sodium edetate; and wherein said pH controlling agent is sodium hydroxide.

28. (Previously presented) The aqueous liquid preparation according to claim 27, wherein the pH is from about 7 to about 9.

29. (Previously presented) The aqueous liquid preparation according to claim 28, wherein the pH is from about 7.5 to about 8.5.

30. (Cancelled)

31. (Previously presented) The aqueous liquid preparation according to claim 23, wherein the concentration of the 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt is about 0.2 w/v %.

32. (Previously presented) The aqueous liquid preparation according to claim 31, wherein the concentration of the tyloxapol is about 0.3 w/v %.

33. (Previously presented) The aqueous liquid preparation according to claim 32, wherein the formulation further includes one or more additives selected from the group consisting of a preservative, buffer, thickener, stabilizer, chelating agent, and pH controlling agent.

34. (Previously presented) The aqueous liquid preparation according to claim 33, wherein said preservative is benzalkonium chloride; wherein said buffer is boric acid and/or sodium borate; wherein said thickener is polyvinylpyrrolidone; wherein said stabilizer is sodium sulfite; wherein said chelating agent is sodium edetate; and wherein said pH controlling agent is sodium hydroxide.

35. (Cancelled)

36. (Previously presented) The aqueous liquid preparation according to claim 31, wherein the concentration of the tyloxapol is about 0.02 w/v %.

37. (Previously presented) The aqueous liquid preparation according to claim 36, wherein the formulation further includes one or more additives selected from the group

consisting of a preservative, buffer, thickener, stabilizer, chelating agent, and pH controlling agent.

38. (Previously presented) The aqueous liquid preparation according to claim 37, wherein said preservative is benzalkonium chloride; wherein said buffer is boric acid and/or sodium borate; wherein said thickener is polyvinylpyrrolidone; wherein said chelating agent is sodium edetate; and wherein said pH controlling agent is sodium hydroxide.

39. (Withdrawn-currently amended) 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, to obtain an aqueous liquid preparation comprising at least the following two components, the first component comprising 2-amino-3-(4- bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof, and the second component comprising tyloxapol or polyethylene glycol monostearate, wherein said liquid preparation is in the form of an eye drop.

40. (Withdrawn-currently amended) A method for inhibiting decrease in preservative effect of a preservative in an aqueous liquid preparation of 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable 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, to obtain an aqueous liquid preparation comprising at least the following two components, the first component comprising 2-amino-3-(4- bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof, and the second component comprising tyloxapol or

polyethylene glycol monostearate, together with a preservative, wherein said liquid preparation is in the form of an eye drop.

41. (Currently amended) An aqueous liquid preparation consisting essentially of ~~at least~~ the following two components, wherein the first component ~~comprising~~ is 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof, and the second component ~~comprising~~ is an alkyl aryl polyether alcohol type polymer or a polyethylene glycol fatty acid ester, wherein said liquid preparation is in the form of an eye drop.

42. (Previously presented) The aqueous liquid preparation according to claim 41, wherein the alkyl aryl polyether alcohol type polymer is tyloxapol;

wherein the concentration of the tyloxapol is selected from a range of about 0.01 w/v % to about 0.5 w/v %; and

wherein the concentration of the 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof is selected from a range of about 0.01 to about 0.5 w/v %.

43. (Previously presented) The aqueous liquid preparation according to claim 42, wherein the pharmacologically acceptable salt of 2-amino-3-(4-bromobenzoyl)phenylacetic acid is a sodium salt.

44. (Previously presented) The aqueous liquid preparation according to claim 43, wherein the concentration of the 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt is selected from a range of about 0.05 to about 0.2 w/v %.

45. (Previously presented) The aqueous liquid preparation according to claim 44, wherein the concentration of the tyloxapol is selected from a range of about 0.01 w/v % to about 0.3 w/v %.

46. (Previously presented) The aqueous liquid preparation according to claim 45, wherein the concentration of the 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt is about 0.1 w/v %.

47. (Previously presented) The aqueous liquid preparation according to claim 46, wherein the concentration of the tyloxapol is about 0.02 w/v %.

48. (Previously presented) The aqueous liquid preparation according to claim 47, wherein the formulation further includes one or more additives selected from the group consisting of a preservative, buffer, thickener, stabilizer, chelating agent, and pH controlling agent.

49. (Previously presented) The aqueous liquid preparation according to claim 48, wherein said preservative is benzalkonium chloride; wherein said buffer is boric acid and/or sodium borate; wherein said thickener is polyvinylpyrrolidone; wherein said stabilizer is sodium sulfite; wherein said chelating agent is sodium edetate; and wherein said pH controlling agent is sodium hydroxide.

50. (Previously presented) The aqueous liquid preparation according to claim 49, wherein the pH is from about 7 to about 9.

51. (Previously presented) The aqueous liquid preparation according to claim 50, wherein the pH is from about 7.5 to about 8.5.

52. (Cancelled)

53. (Previously presented) The aqueous liquid preparation according to claim 45, wherein the concentration of the 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt is about 0.2 w/v %.

54. (Previously presented) The aqueous liquid preparation according to claim 53, wherein the concentration of the tyloxapol is about 0.3 w/v %.

55. (Previously presented) The aqueous liquid preparation according to claim 54, wherein the formulation further includes one or more additives selected from the group consisting of a preservative, buffer, thickener, stabilizer, chelating agent, and pH controlling agent.

56. (Previously presented) The aqueous liquid preparation according to claim 55, wherein said preservative is benzalkonium chloride; wherein said buffer is boric acid and/or sodium borate; wherein said thickener is polyvinylpyrrolidone; wherein said stabilizer is sodium sulfite; wherein said chelating agent is sodium edetate; and wherein said pH controlling agent is sodium hydroxide.

57. (Cancelled)

58. (Previously presented) The aqueous liquid preparation according to claim 53, wherein the concentration of the tyloxapol is about 0.02 w/v %.

59. (Previously presented) The aqueous liquid preparation according to claim 58, wherein the formulation further includes one or more additives selected from the group

consisting of a preservative, buffer, thickener, stabilizer, chelating agent, and pH controlling agent.

60. (Previously presented) The aqueous liquid preparation according to claim 59, wherein said preservative is benzalkonium chloride; wherein said buffer is boric acid and/or sodium borate; wherein said thickener is polyvinylpyrrolidone; wherein said chelating agent is sodium edetate; and wherein said pH controlling agent is sodium hydroxide.

61. (Withdrawn-currently amended) 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, to obtain an aqueous liquid preparation consisting essentially of at least the following two components, the first component comprising 2-amino-3-(4- bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof, and the second component comprising tyloxapol or polyethylene glycol monostearate, wherein said liquid preparation is in the form of an eye drop.

62. (Currently amended) A method for inhibiting decrease in preservative effect of a preservative in an aqueous liquid preparation of 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable 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, to obtain an aqueous liquid preparation consisting essentially of at least the following two components, the first component comprising 2-amino-3-(4- bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate

thereof, and the second component comprising tyloxapol or polyethylene glycol monostearate, together with a preservative, wherein said liquid preparation is in the form of an eye drop.

63. (Currently amended) An aqueous liquid preparation consisting of the following two components, the first component ~~comprising~~ is 2-amino-3-(4- bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof, and the second component ~~comprising~~ is an alkyl aryl polyether alcohol type polymer or a polyethylene glycol fatty acid ester, and water, and optionally at least one preservative, isotonic, buffer, thickener, stabilizer, chelating agent, pH controlling agent, or perfume, wherein said liquid preparation is in the form of an eye drop.

REMARKS

Favorable reconsideration is respectfully solicited in view of the following remarks.

Initially, Applicant wishes to express its sincere thanks for the courtesy and cooperation provided to its undersigned representative by Examiner Timothy Thomas and Supervisory Examiner Ardin Marschel during the personal interview held on November 20, 2008. The following is a summary of the items discussed during the interview.

Claims 19, 39, 40, 41, 61, 62 and 63 have been amended to require that the aqueous liquid preparation is in the form of an eye drop. Claims 30, 35, 52 and 57 have accordingly been cancelled.

Claim 41 has been amended to delete "at least" and to change "comprising" to – is –.

Claim 63 has been amended to change "comprising" to – is – and to add --and water --.

Turning to the Official Action, Applicants acknowledge with thanks the Examiner's indication that numerous former grounds of rejection have been withdrawn in view of Applicants' last response.

On page 3, claims 19-29, 31-34, 36-38, 41-51, 53-56, 58-60 and 63 are rejected under 35 U.S.C. 103 as obvious over Gamache et al. (WO 01/15677) in view of ISTA or Nolan et al. This ground of rejection is respectfully traversed as applied to the amended claims.

Claims 19, 39, 40, 41, 61, 62 and 63 have been amended to require that the aqueous liquid preparation is in the form of an eye drop according to claims 30, 35, 52 and 57. None of claims 30, 35, 52 or 57 were encompassed by the rejection.

Accordingly this ground of rejection is deemed to be overcome.

Furthermore, Applicants take the opportunity to provide additional remarks for the Examiner's consideration against a potential 103 rejection based upon a different combination of references.

The subject matter of the claimed invention is directed to an eye drop having a specific combination of 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.

On the other hand, Gamache et al. do not disclose or suggest this specific combination. The cited reference is directed to compositions comprising of 5-HT_{1D} and/or HT_{1B} agonists. The cited reference states that these agonists may be combined with an extensive list of other pharmaceutical agents, i.e. (1) anti-microbial agent, (2) anti-inflammatory agents or (3) anti-allergy agent (please see page 6, lines 1-3 of Gamache). Gamache et al. only describes "bromfenac" as one of many examples of anti-inflammatory agents enumerated on page 12, lines 11-24. Gamache et al. does not concretely describe nor suggest the claimed preparation containing bromfenac.

Further, tyloxapol (0.05% w/v) is only mentioned as being added to an 1B/1D agonist (0.1-1.0% w/v) and moxifloxacin (0.3% w/v) in Example 4 (an Example of an otic/nasal suspension). There is no explanation about tyloxapol in the description of Gamache et al. or why it is included. Moreover in this Example, moxifloxacin is incorporated as a well-known antibacterial agent but is not an anti-inflammatory agent like bromfenac. Thus it is unclear from Gamache et al. why tyloxapol is added to the otic/nasal suspension containing 1B/1D agonist and moxifloxacin.

"Tyloxapol" described in Example 4 is just a single word description and does not give any clues and hints to the present invention. Therefore, the word "tyloxapol" described only in Example 4 does not destroy the novelty of the present invention.

Further, Gamache et al. is silent about an alkyl aryl polyether alcohol type polymer or a polyethylene glycol fatty acid ester component according to the claimed eye drop.

Thus the disclosure of Gamache et al. would suggest to the skilled artisan thousands of possible combinations of ingredients to include with an IB/ID agonist. Such disclosure does not lead the artisan to the claimed specific combination nor does such disclosure render the claimed combination obvious. The prior art must motivate one skilled in the art to make the claimed combination. There is no teachings or suggestion in Gamache of selecting bromfenac in combination with an alkyl aryl polyether alcohol type polymer or a polyethylene glycol fatty acid ester.

Furthermore, Gamache et al. is directed to compositions for relieving otic pain (abstract) by apply the compositions to the ear or nasally (page 10, lines 6-9 and Example 4). There is no teaching or motivation to make the claimed eye drop.

Regarding claims 41-51, 53-56 and 58-60, the claims are directed to an eye drop which consists essentially of the recited specific combination of ingredients. The claim recites the transitional phrase "consisting essentially of" means that the claim is open to include the specified ingredients and additional ingredients that do not materially affect the basic and novel characteristics of the claimed invention. See M.P.E.P. 2111.03.

It is respectfully submitted that the principal IB/ID agonist of the Gamache composition would affect the basic novel properties of the claimed preparation.

One skilled in the art would not have been motivated to modify the Gamache et al. composition in view of ISTA and Nolan, to arrive at the claimed eye drop. The primary object of Gamache et al. is to make a composition containing an IB/ID agonist. The artisan would not have been motivated by the reference to make a composition lacking the IB/ID agonist. An IB/ID agonist is excluded from claims 41-51, 53-56 and 58-60 by the "consisting essentially of" transitional phrase.

Regarding claim 63, the claim is limited to an eye drop which "consists of" the recited bromfenac, recited an alkyl aryl polyether alcohol type polymer or a polyethylene glycol fatty acid ester, and water. Such claim explicitly excludes other ingredients, such as an IB/ID agonist.

For the foregoing reasons, Applicant submits that the present invention is unobvious from Gamache et al. and ISTA or Nolan to those skilled in the art.

Claims 41-60 and 63 are rejected under 35 USC 112, second paragraph, as being indefinite for the reasons set forth on pages 6-7 of the Action.

Based upon the Examiner's remarks during the personal interview, it is believed that this ground of rejection is overcome by the foregoing amendments.

Claims 19-38, 41-60 and 63 are rejected under 35 USC 103 as being unpatentable over Hellberg et al. and Nolan et al. This ground of rejection is respectfully traversed as applied to the amended claims.

The Examiner asserts that it would have been obvious to substitute the compounds having anti-inflammatory and anti-oxidant activity used in the ophthalmic compositions of Hellberg et al. with bromfenac used in the dermal applications disclosed in Nolan et al. Applicants respectfully disagree.

The intended purpose of the invention disclosed in Hellberg et al. is to provide "[c]ompounds having anti-inflammatory ***and*** antioxidant activity." See Hellberg et al., Abstract (emphasis added); see also Hellberg at column 2, lines 13-18 ("***The present invention provides*** new compounds having potent anti-inflammatory ***and*** anti-oxidant activity.") (emphasis added). Indeed, Hellberg et al. explicitly state that the principle of operation of the anti-inflammatory and antixodixant compounds is to provide a two-pronged therapeutic approach not previously available in the art:

> The compounds of the present invention are capable of protecting against cellular damage by a wide range of insults. Since the compounds provide this protection by decreasing free radical or oxidative damage, reducing cyclooxygenase or lipoxygenase mediated inflammation, and improving site delivery, this therapy represents an improved two-pronged approach to cytoprotection.

See Hellberg et al. at Column 2, lines 57-63. Therefore, the intended purpose of the invention disclosed in Hellberg et al. is to provide compounds with not only anti-inflammatory activity, but also anti-oxidant activity for improved therapeutic functionality:

> The compounds also include an anti-oxidant component. As oxidative stress has been implicated in inflammatory responses, the presence of an anti-oxidant will further help treat the target tissue.
>
> The compounds of the present invention also exhibit properties present only in the combined molecule, ***not in the individual components***. One such property is the inhibitory efficacy against 5-lipoxygenase, an enzyme known to be involved in inflammation.

See Hellberg et al. at Column 2, lines 38-45 (emphasis added).

The USPTO has made clear that "[i]f [the] proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification." See MPEP section 2143.01 V, citing *In re*

Gordon, 733 F.2d 900 (Fed. Cir. 1984). Additionally, section 2143.01 VI of the MPEP plainly states: "The proposed modification cannot change the principle of operation of a reference. If the proposed modification or combination of the prior art would change the principle of operation of the prior art invention being modified, then the teachings of the references are not sufficient to render the claims *prima facie* obvious." See also *In re Ratti*, 270 F.2d 810, 123 USPQ 349 (CCPA 1959).

Here, the Examiner asserts that it would have been obvious to substitute the anti-inflammatory and anti-oxidant compounds disclosed in Hellberg et al. with bromfenac as disclosed in Nolan et al. because of "the art recognized equivalent activity of bromfenac as an anti-inflammatory agent in topical usage." See Official Action date July 18, 2008 at page 9. But as indicated in the Official Action and in Hellberg et al., bromfenac is an anti-inflammatory and not an antioxidant. The proposed substitution of the dual action anti-inflammatory and anti-oxidant compounds disclosed in Hellberg et al. with bromfenac would render the Hellberg et al. invention unsatisfactory for its intended purpose of providing "compounds having potent anti-inflammatory and anti-oxidant activity." The proposed substitution would result in a bromfenac composition having only anti-inflammatory activity. This proposed modification would radically change the principle of operation of Hellberg et al. from "an improved two-pronged approach to cytoprotection" to a mere one-pronged approach based on anti-inflammatory action alone.

Therefore, because the proposed substitution of the anti-inflammatory and anti-oxidant compounds disclosed in Hellberg et al. with bromfenac as disclosed in Nolan et al. would render the Hellberg et al. invention unsatisfactory for its intended purpose and radically change the principle of operation of Hellberg et al., Applicants respectfully submit a prima facie case of obviousness cannot be based on the combination of Hellberg et al. and Nolan et al.

In addition to the argument that the proposed modification changes the principle operation and intended purpose of Hellberg et al., Applicants submit that Hellberg et al. explicitly teach away from the use of a compound, such as bromfenac, having only anti-inflammatory activity. Hellberg et al. clearly recite deficiencies in the use of non-steroidal anti-inflammatory agents such as bromfenac:

> Non-steroidal anti-inflammatory agents (NSAIA) have been used for the treatment of inflammatory disorders. The following references may be referred to for further background concerning this use of NSAIAs:
>
> Ophthalmoscope, volume 8, page 257 (1910);
>
> FASEB Journal, volume 1, page 89 (1987); and
>
> Inflammation and Mechanisms and Actions of Traditional Drugs, vol. I Anti-inflammatory and Anti-rheumatic drugs. Boca Raton, Fla., CRC Press, (1985).
>
> However, ***there are some problems associated with NSAIA treatment including delivery to the appropriate site of action and side effects*** (Goodman and Gilman's The Pharmacological Basis of Therapeutics, pages 638-669, Pergman Press, NY (1990)).

See Hellberg et al. at Column 1, lines 28-37 (emphasis added).

According to the USTPO guidelines, "[i]t is improper to combine references where the references teach away from their combination." See MPEP § 2145, citing *In re Grasselli*, 713 F.2d 731, 743 (Fed. Cir. 1983); see also *McGinley v. Franklin Sports, Inc.*, 262 F.3d 1339, 1354 (Fed.Cir. 2001) ("It is well-established that references which "teach away cannot serve to create a prima facie case of obviousness.") (citations omitted).

Here, Hellberg et al. plainly state that NSAIA treatment is associated with "problems" such as "side effects" and "delivery to the appropriate site of action." In light of this teaching away from the use of a non-steroidal anti-inflammatory agent (NSAIA), one skilled in the art would not substitute bromfenac, a known NSAIA, for the anti-inflammatory and anti-oxidant compounds disclosed in Hellberg et al. Therefore, because Hellberg et al. teach away from the use of bromfenac, Applicants respectfully submit a prima facie case of obviousness cannot be based on the combination of Hellberg et al. and Nolan et al.

For the reasons detailed above, Applicants respectfully request withdrawal of the rejection of claims 19-38, 41-60 and 63 under 35 USC 103 as being unpatentable over Hellberg et al. and Nolan et al.

Lastly, claims 19-38 are provisionally rejected on the ground of non-statutory obviousness-type double patenting as being unpatentable over claims 1-43 of copending

application Serial No. 11/755,662.

The Examiner is respectfully requested to hold this provisional ground of rejection in abeyance until a later date. Upon overcoming all other grounds of rejection, it is respectfully submitted that this provisional ground of rejection should be withdrawn and the application passed on to allowance.

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

Respectfully submitted,

Shirou SAWA et al.

By: 

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

WMC/dlk
Washington, D.C. 20006-1021
Telephone (202) 721-8200
Facsimile (202) 721-8250
January 15, 2009

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of	:	**Confirmation No. 1756**
Shirou SAWA et al.	:	Attorney Docket No. 2005_0232A
Serial No. 10/525,006	:	Group Art Unit 1614
Filed March 28, 2005	:	Examiner Timothy P. Thomas

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

Mail Stop: AMENDMENT

PATENT OFFICE FEE TRANSMITTAL FORM

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

Sir:

Attached hereto is a check in the amount of $1,110.00 to cover Patent Office fees relating to filing the following attached papers:

Petition for Extension of Time $1,110.00

Other: ..... $

The Commissioner is authorized to charge any deficiency or to credit any overpayment associated with this communication to Deposit Account No. 23-0975, with the EXCEPTION of deficiencies in fees for multiple dependent claims in new applications.

Respectfully submitted,

Shirou SAWA et al.

By _____
Warren M. Cheek
Registration No. 33,367
Attorney for Applicants

WMC/dlk
WENDEROTH, LIND & PONACK, L.L.P.
2033 K St., N.W., Suite 800
Washington, D.C. 20006-1021
Telephone (202) 721-8200
January 15, 2009

[Check No. 88932]

2005_0232A

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of	:	**Confirmation No. 1756**
Shirou SAWA et al.	:	Attorney Docket No. 2005_0232A
Serial No. 10/525,006	:	Group Art Unit 1614
Filed March 28, 2005	:	Examiner Timothy P. Thomas

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

Mail Stop: AMENDMENT

PATENT OFFICE FEE TRANSMITTAL FORM

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

Sir:

Attached hereto is a check in the amount of $1,110.00 to cover Patent Office fees relating to filing the following attached papers:

Petition for Extension of Time $1,110.00

Other: ..... $

The Commissioner is authorized to charge any deficiency or to credit any overpayment associated with this communication to Deposit Account No. 23-0975, with the EXCEPTION of deficiencies in fees for multiple dependent claims in new applications.

Respectfully submitted,

Shirou SAWA et al.

By _____
Warren M. Cheek
Registration No. 33,367
Attorney for Applicants

WMC/dlk
WENDEROTH, LIND & PONACK, L.L.P.
2033 K St., N.W., Suite 800
Washington, D.C. 20006-1021
Telephone (202) 721-8200
January 15, 2009

[Check No. 88922]

2005_0232A

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of	:	**Confirmation No. 1756**
Shirou SAWA et al.	:	Attorney Docket No. 2005_0232A
Serial No. 10/525,006	:	Group Art Unit 1614
Filed March 28, 2005	:	Examiner Timothy P. Thomas

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

Mail Stop: Amendment

PETITION FOR EXTENSION OF TIME

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

Sir:

Petition hereby is made for a three month extension of time to respond to the communication of July 18, 2008.

The fee of $1,110.00 is
(X) submitted herewith.
() to be charged to Deposit Account No. 23-0975. A duplicate copy of this Petition is enclosed.

() Small entity status of this application is established by a Small Entity Status Assertion which
- () is enclosed.
- () has been previously submitted.
- () has been previously asserted.

The Commissioner is authorized to charge any deficiency or to credit any overpayment associated with this communication to Deposit Account No. 23-0975, with the EXCEPTION of deficiencies in fees for multiple dependent claims in new applications.

Respectfully submitted,
Shirou SAWA et al.

By _____
Warren M. Cheek
Registration No. 33,367
Attorney for Applicants

WMC/dlk
Washington, D.C. 20006-1021
Telephone (202) 721-8200
Facsimile (202) 721-8250
January 15, 2009

01/16/2009 SKOHAMME 00000061 10525006
01 FC:1253 1110.00 OP

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
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	Filing Date	☐ To be Mailed
10/525,006	03/28/2005	

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY ☐ RATE ($)	SMALL ENTITY ☐ FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =		OR	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =			X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT	01/15/2009	(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))	* 41	Minus	** 45	= 0	X $ =		OR	X $52=	0
	Independent (37 CFR 1.16(h))	* 7	Minus	***7	= 0	X $ =		OR	X $220=	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:
/MOLIKI I. MAY/

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number	Filing Date	☐ To be Mailed
10/525,006	03/28/2005	

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY ☐ RATE ($)	SMALL ENTITY ☐ FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =		OR	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =			X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT	01/15/2009	(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))	* 41	Minus	** 45	= 0	X $ =		OR	X $52=	0
	Independent (37 CFR 1.16(h))	* 7	Minus	***7	= 0	X $ =		OR	X $220=	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:
/MOLIKI I. MAY/

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.
10/525,006	03/28/2005	Shirou Sawa	2005_0232A	1756

513 7590 12/03/2008

WENDEROTH, LIND & PONACK, L.L.P.
2033 K STREET N. W.
SUITE 800
WASHINGTON, DC 20006-1021

EXAMINER	
THOMAS, TIMOTHY P	

ART UNIT	PAPER NUMBER
1614	

MAIL DATE	DELIVERY MODE
12/03/2008	PAPER

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.

Interview Summary	Application No.	Applicant(s)	
	10/525,006	SAWA ET AL.	
	Examiner	Art Unit	
	TIMOTHY P. THOMAS	1614	

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

(1) *TIMOTHY P. THOMAS*. (3)*Warren Cheek*.

(2) *Ardin Marschel*. (4)*Naoko Kishida*.

Date of Interview: *20 November 2008*.

Type: a)☐ Telephonic b)☐ Video Conference
c)☒ Personal [copy given to: 1)☐ applicant 2)☐ applicant's representative]

Exhibit shown or demonstration conducted: d)☐ Yes e)☒ No.
If Yes, brief description: _____.

Claim(s) discussed: *19 and 41*.

Identification of prior art discussed: *Gamache, et al. (WO 01/15677 A2); Nolan, et al. ("The topical anti-inflammatory and analgesic properties of bromfenic in rodents; Agents and Actions; 1988 Aug; 25(1-2):77-85); Hellberg et al. (US 5,998,465)*.

Agreement with respect to the claims f)☐ was reached. g)☒ was not reached. h)☐ N/A.

Substance of Interview including description of the general nature of what was agreed to if an agreement was reached, or any other comments: *Potential claim amendments were discussed that might potentially overcome the prior art-based rejections; potential designs of experimental studies were also discussed that might yield unexpected results to overcome the 103 rejections*.

(A fuller description, if necessary, and a copy of the amendments which the examiner agreed would render the claims allowable, if available, must be attached. Also, where no copy of the amendments that would render the claims allowable is available, a summary thereof must be attached.)

THE FORMAL WRITTEN REPLY TO THE LAST OFFICE ACTION MUST INCLUDE THE SUBSTANCE OF THE INTERVIEW. (See MPEP Section 713.04). If a reply to the last Office action has already been filed, APPLICANT IS GIVEN A NON-EXTENDABLE PERIOD OF THE LONGER OF ONE MONTH OR THIRTY DAYS FROM THIS INTERVIEW DATE, OR THE MAILING DATE OF THIS INTERVIEW SUMMARY FORM, WHICHEVER IS LATER, TO FILE A STATEMENT OF THE SUBSTANCE OF THE INTERVIEW. See Summary of Record of Interview requirements on reverse side or on attached sheet.

/Timothy P Thomas/ Examiner, Art Unit 1614	

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.
10/525,006	03/28/2005	Shirou Sawa	2005_0232A	1756

513 7590 07/18/2008

WENDEROTH, LIND & PONACK, L.L.P.
2033 K STREET N. W.
SUITE 800
WASHINGTON, DC 20006-1021

EXAMINER	
THOMAS, TIMOTHY P	

ART UNIT	PAPER NUMBER
1614	

MAIL DATE	DELIVERY MODE
07/18/2008	PAPER

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.

Office Action Summary	Application No.	Applicant(s)	
	10/525,006	SAWA ET AL.	
	Examiner	Art Unit	
	TIMOTHY P. THOMAS	1614	

-- 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 *26 March 2008*.

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

3)☐ 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

4)☒ Claim(s) *19-63* is/are pending in the application.

4a) Of the above claim(s) *39,40,61 and 62* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *19-38,41-60 and 63* is/are rejected.

7)☒ Claim(s) *41-60* is/are objected to.

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

Application Papers

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

10)☐ 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).

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

Priority under 35 U.S.C. § 119

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) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/26/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. New claims 61-62 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 8/20/2007.

Response to Arguments

2. Applicants' arguments, filed 3/26/2008, have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

3. Applicant's arguments, see pp. 11-14, filed 3/26/2008, with respect to the rejections of claims 19-24 and 31, of claim 19 and of claims 19-38 under 35 USC 102 have been fully considered and are persuasive. The rejections of claims 19-24 and 31, 19 and 19-38 have been withdrawn.

Applicant's arguments that neither Gamache nor Dobrozsi concretely describe the combination of bromfenac and tyloxapol, recited in the amended claims, are persuasive. Therefore the rejections based on Gamache and Dobrozsi are withdrawn. Applicant's argument that Sawa does not have a proper 102(e) date is also persuasive.

4. Applicant's arguments, see pp. 15-17, filed 3/26/2008, with respect to rejection of claims 19-29, 31-34 and 36-38 under 35 USC 103 have been fully considered and are persuasive. The rejection of claims 19-29, 31-34 and 36-38 has been withdrawn.

Applicant's arguments that neither Gamache nor Dobrozsi concretely describe the combination of bromfenac and tyloxapol, recited in the amended claims, are persuasive. Therefore the rejections based on Gamache and Dobrozsi are withdrawn. Applicant's arguments that Sawa does not have a 102(e) date is persuasive.

5. Applicant's arguments with respect to the rejection of claims 19-29, 31-34 and 36-38 as being unpatentable over Gamache and ISTA Pharmaceuticals or Nolan have been fully considered but they are not persuasive:

6. Claims 19-29, 31-34, 36-38, 41-51, 53-56, 58-60 and 63 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gamache, et al. (WO 01/15677 A2; 03/2001; previously cited) and ISTA Pharmaceuticals ("New Drug Applications: Xibrom", http://www.drugs.com/nda/xibrom_040525.html, accessed online 9/19/2007; previously cited) or Nolan, et al. ("The topical anti-inflammatory and analgesic properties of bromfenic in rodents; Agents and Actions; 1988 Aug; 25(1-2):77-85; provided with Interview Summary).

The rejection is maintained for the reasons of record and the following reasons.

Applicant argues that Gamache does not suggest the claimed invention, because Gamache is directed to 5-HT agonists compositions with a great number of other possible ingredients; the reference does not suggest the required combination of bromfenac and tyloxapol. This is not persuasive. Gamache clearly teaches combinations of 5-$HT_{1B/1D}$ agonists with one or more anti-inflammatory agents, dosed concurrently or sequentially with anti-inflammatory agent compositions. (p. 12, lines 9-11); bromfenac is clearly taught as an anti-inflammatory compound specie (p. 12, line

17; claim 11). This implies two different compositions as embodiments: 1) a composition containing a 1B/1D agonist and an anti-inflammatory agent (such as in claims 7, 10-11) and 2) two different compositions, where the first contains only an anti-inflammatory agent as the active compound, the second contains only a 1B/1D agonist as active agent (implied by sequential dosing). Taking Example 4 as the model formulation, it would have been obvious to one of ordinary skill in the art at the time of the invention to substitute bromfenac for Moxifloxin taught in the example, giving an aqueous liquid preparation containing both required ingredients of the instant claims, bromfenac and tyloxapol (along with the 5-$HT_{1B/1D}$ agonists). Alternatively, it would have been obvious to substitute bromfenac for both Moxifloxin and the 1B/1D agonist, giving an aqueous liquid preparation containing both required ingredients of the instant claims, bromfenac and tyloxapol (without a 5-$HT_{1B/1D}$ agonist). The motivation to prepare the combination formulation (with two active ingredients) would have been for the treatment of otic inflammatory reactions and responses, taught by Gamache (on p. 12, lines 8-11). The motivation to prepare the single active formulation (without a 5-$HT_{1B/1D}$ agonist) would have been for the sequential treatment of otic inflammatory reactions and responses, taught by Gamache. The motivation to select bromfenac as the anti-inflammatory agent would have been the art-recognized usefulness for the purpose of treating inflammatory reactions and responses, recognized by Gamache, and bomfenac sodium at the concentrations of the claims is taught by ISTA Pharmaceuticals and Nolan, also suitable for the purpose of Gamache's formulations. With respect to the tyloxapol concentrations recited in instant claims 25 and 32, of “about 0.02 w/v%” and

"about 0.3 w/v%", the amount taught is considered to be close, if not within the unspecified range implied by "about". Alternatively, it would have been obvious to optimize concentrations of tyloxapol, which one of ordinary skill in the art would have recognized is a surfactant, to optimize the conditions of the formulations for solubility of other ingredients, stability and efficacy in the anti-inflammatory action of the formulation, which would have given tyloxapol concentrations of the instant claims. The motivation would have been the routine optimization of conditions.

Applicant argues that ISTA Pharmaceuticals press release about Xibrom has a different composition than the instant formulation. This point is not at issue; the reference was cited to demonstrate salts and hydrates of bromfenac and concentrations of the instant claims. Applicant also argues the ISTA reference of the Nolan reference in combination with Gamache does not suggest the claimed invention comprising the at least two components. This is not persuasive because Gamache alone suggests the combination of the two required components, as outlined above.

Applicant argues that the combination of a 1B/1D agonist with bromfenac would not read on claims 41-60 because of the recitation of the "consisting essentially of" transitional phrase. This is not persuasive, since the phrase "at least" after "consisting essentially of" in claim 41 opens the subject matter to any additional ingredients. Even if the "at least" were absent from the claim language, the embodiment suggested by Gamache of only one single active anti-inflammatory agent (useful in a sequential treatment method) would obviate such a claim construction. With respect to claim 63, even if the "comprising" language was replaced by "consisting of" language, the

substitution of bromfenac for the active ingredients in Example 4 as suggested by Gamache would produce a composition that reads on the specific components recited in claim 63, assuming water would be required in that claim.

7. Applicant's arguments, see pp. 17-18, with respect to the rejection of claims 19-30 as being unpatentable over Yakuji Nippo Ltd. and Xia; and claims 19-38 as being unpatentable over Yakuji Nippo Ltd., Xia, and Nolan have been fully considered and are persuasive. Therefore, the rejections have been withdrawn. However, upon further consideration, a new ground(s) of rejection is made as follows.

8. Claims 19-38, 41-60 and 63 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-43 of copending Application No. 11/755662.

Claim Rejections - 35 USC § 112

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

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

10. Claims 41-60 and 63 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

This rejection is necessitated by the amendment introducing new claims.

11. With respect to claims 41-60, the recitation of the transitional phrase generally considered to refer to closed claim language, "consisting essentially of" together with the open language term, "at least" in the 1st line of claim 41, is not clear whether open construction or closed construction is meant by the claim; additionally the language of

the 1st and 2nd components, “comprising”, an open construction term is also unclear and inconsistent with the closed construction phrase, “consisting essentially of”. It is not clear whether formulations containing the recited components and additional components would fall within or outside of the metes and bounds of the instant claims. For other rejections the phrase "consisting essentially of at least" is construed to have the same meaning as "comprising", consistent with the broadest reasonable interpretation of these claims.

12. With respect to claim 63, the recitation of the transitional phrase, “consisting of" the two components, each of which use the term, “comprising” to recite the compounds present in each components, does not make clear whether the claim construction is closed or open; i.e., it is not clear whether a formulation containing one compound from the 1st component, one compound from the 2nd component, one or more of the optional components recited and at least one non-component compound (not recited in the claim), such as water or an alcohol, would fall within the scope of or be excluded from the subject matter of the claim. For prior art rejections, the claims are construed in the broader meaning, i.e., the presence of "comprising” in the claim has the meaning of open ended claim construction.

13. Additionally, claim 63 recites “an aqueous liquid preparation” consisting of two required components, and optionally containing at least one additional component, none of the required or optional components recite water. The presence of an “aqueous” preparation along with the absence of water is inconsistent, and does not make clear whether water is required, optional or absent.

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

14. Claims 19-38, 41-60 and 63 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hellberg et al. (US 5,998,465; 1999) and Nolan, et al. ("The topical anti-inflammatory and analgesic properties of bromfenac in rodents; Agents and Actions; 1988 Aug; 25(1-2):77-85; cited with previous Interview Summary).

15. Hellberg teaches pharmaceutical compositions of anti-inflammatory compounds (abstract); the compounds include a non-steroidal anti-inflammatory moiety (NSAIA) and an antioxidant moiety linked through an ester bond formed by the carboxylic acid moiety of the NSAIA (col. 2, lines 20-24); NSAIA moieties include bromfenac (col. 3, line 57; claim 5); examples 2 and 3 (col. 11) teach topical ophthalmic formulations useful for treating inflammation, both of these formulations include tyloxapol at 0.01-0.05 w/v %, HPMC (thickener), benzalkonium chloride (preservative), edetate disodium (chelating agent) (col. 11, Examples 2-3); the pH is adjusted to 7.4 (about 7.5; col. 11, line 64); topical formulations administered by drops (eyedrops; col. 10, lines 15-18). Hellberg does not teach bromfenac (only the ester of bromfenac). Nolan teaches bromfenac (the sodium salt, sesquihydrate form) was effective as a topical analgesic at concentrations of 0.1-0.32 % in mice and more potent than the other drugs tested (abstract). It would have been obvious for one of ordinary skill in the art at the time of the invention to substitute bromfenac, taught by Nolan for the compounds of Hellberg in the example formulation giving formulations of the instant claims and to select concentrations of

bromfenac sodium, sesquihydrate of 0.1, about 0.2 and about 0.32 %, in the invention of Gamache, since these values have demonstrated efficacy for topical use. It would also have been obvious to adjust the concentration of tyloxapol, to optimize the formulations for the effect would on the solubility and stability of the aqueous preparations, which would have resulted in the effective tyloxapol concentrations of about 0.02 and 0.3 w/v%, recited in claims 25 and 32. The motivation to substitute bromfenac in the Hellberg formulations would have bee the art-recognized equivalent activity of bromfenac as an anti-inflammatory agent in topical usage. The motivation to adjust concentrations would have been the routine optimization of these topical ophthalmic formulations for anti-inflammatory use in the eye.

Double Patenting

16. A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

17. Claims 41-60 are objected to under 37 CFR 1.75 as being a substantial duplicate of claims 19-38. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

This objection is necessitated by the amendment adding new claims. Claim 41 uses the transitional phrase in the preamble, "consisting essentially of at least", whereas claim 19 uses the transitional phrase, "comprising"; all other wording is identical. "Consisting essentially of" is generally closed language, excluding components not recited in the claim. However, the presence of the open language term, "at least" removes the closed language of "consisting essentially of", giving the meaning that the recited components are required, but additional components no recited may optionally be present, which is the same meaning possessed by the term, "comprising". Therefore, though the two sets of claims use slightly different wording, the meanings are the same.

Conclusion

18. No claim is allowed.

19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to TIMOTHY P. THOMAS whose telephone number is (571)272-8994. The examiner can normally be reached on Monday-Thursday 6:30 a.m. - 5:00 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on (571) 272-0718. 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.

/Timothy P Thomas/
Examiner, Art Unit 1614

/Ardin Marschel/
Supervisory Patent Examiner, Art Unit 1614

Notice of References Cited	Application/Control No. 10/525,006	Applicant(s)/Patent Under Reexamination SAWA ET AL.	
	Examiner TIMOTHY P. THOMAS	Art Unit 1614	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
*	A	US-5,998,465	12-1999	Hellberg et al.	514/432
	B	US-			
	C	US-			
	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					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

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

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	10525006	SAWA ET AL.
	Examiner	Art Unit
	Thomas, Timothy P	1614

SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES		
Search Notes	Date	Examiner
WEST	9/19/2007	TPT
Google	9/19/2007	TPT
STN Search	9/19/2007	TPT
PubMed	9/19/2007	TPT
Inventor Name Search	9/19/2007	TPT
IDS References	9/19/2007	TPT
PubChem	7/2/2008	TPT
WEST	7/2/2008	TPT
PubMed	7/2/2008	TPT
IDS references	7/2/2008	TPT

INTERFERENCE SEARCH			
Class	Subclass	Date	Examiner

Sheet 1 of 1

INFORMATION DISCLOSURE STATEMENT

FORM PTO 1449 (*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: March 26, 2008

ATTY DOCKET NO.	SERIAL NO.
2005_0232A	10/525,006

APPLICANT	
Shirou SAWA et al.	

FILING DATE	GROUP
March 28, 2005	1614

U.S. PATENT DOCUMENTS

*EXAMINER INITIAL		DOCUMENT NUMBER	DATE	NAME	CLASS	SUBCLASS	FILING DATE IF APPROPRIATE
	AA						
	AB						
	AC						
	AD						
	AE						
	AF						
	AG						
	AH						
	AI						

FOREIGN PATENT DOCUMENTS

		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION YES	TRANSLATION NO
	BA							
	BB							
	BC							
	BD							
	BE							

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

	CA	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.
	CB	Complete English translation of New Drugs in Japan, 2001, 2001 Edition, Published by Yakuji Nippo Ltd., May 11, 2001, pp. 27-29.
	CC	

EXAMINER	/Timothy Thomas/	DATE CONSIDERED	07/02/2008

*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.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /TPT/

Search PubChem Compound for bromfenac Preview

Limits Preview/Index History Clipboard Details

- Search History will be lost after eight hours of inactivity.
- Search numbers may not be continuous; all searches are represented.
- To save search indefinitely, click query # and select Save in My NCBI.
- To combine searches use #search, e.g., #2 AND #3 or click query # for more options.

Search	Most Recent Queries	Time	Result
#22	Search bromfenac	11:24:14	4
#21	Search tyloxapol	11:24:06	2

Clear History

- Search History will be lost after eight hours of inactivity.
- Search numbers may not be continuous; all searches are represented.
- To save search indefinitely, click query # and select Save in My NCBI.
- To combine searches use #search, e.g., #2 AND #3 or click query # for more options.

Search	Most Recent Queries	Time	Result
#18	Search tyloxapol (eye or ocular or ophthalmic)	07:10:33	2
#16	Search tyloxapol	07:09:50	286
#15	Search bromfenac tyloxapol	07:09:36	0
#13	Search bromfenac (eye or ocular or ophthalmic)	07:08:24	22
#3	Search bromfenac	07:06:39	82
#1	Search tyloxapol	06:33:18	286

Clear History

WEST Search History for Application 10525006

Creation Date: 2008070311:22

Query	DB	Op.	Plur.	Thes.	Date
Bromfenac or Duract or (BROMFENAC SODIUM) or (AHR 10282B) or (Bromfenac monosodium salt sesquihydrate) or (Sodium (2-amino-3-(p-bromobenzoyl)phenyl)acetate sesquihydrate) or (Benzeneacetic acid, 2-amino-3-(4-bromobenzoyl)-, monosodium salt, hydrate (2:3)) or (Benzeneacetic acid, 2-amino-3-(4-bromobenzoyl)-, monosodium salt, sesquihydrate) or (120638-55-3) or (sodium 2-(2-amino-3-(4-bromobenzoyl)phenyl)acetate)	PGPB, USPT, USOC, EPAB, JPAB, DWPI	ADJ	YES	ASSIGNEE	07-02-2008
Macrocyclon or Tyloxapol or Superinone or Alevaire or Tyloxypal or Superiuone or Enuclene or Exosurf or (Triton A-20) or (Triton WR 1339) or (Triton WR-1339 Triton W.R.1339) or Tiloxapol or Tyloxapolum or AIDS094886 or (AIDS-094886) or (NSC 90255) or (p-Isooctylpolyoxyethylenephenol formaldehyde polymer) or (Oxyethylated tertiary octyl-phenol-formaldehyde polymer) or (25301-02-4) or (Phenol, p-(1,1,3,3-tetramethylbutyl)-, polymer with ethylene oxide and formaldehyde) or (4-(1,1,3,3-Tetramethylbutyl)phenol, polymer with formaldehyde & oxirane) or (Formaldehyde, polymer with oxirane and 4-(1,1,3,3-tetra methylbutyl)phenol) or (Formaldehyde, polymer with oxirane and 4-(1,1,3,3-tetramethylbutyl)phenol) or (p-(1,1,3,3-Tetramethylbutyl)phenol polymer with ethylene oxide and formaldehyde) or (Phenol, 4-(1,1,3,3-tetramethylbutyl)-, polymer with formaldehyde and oxirane)	PGPB, USPT, USOC, EPAB, JPAB, DWPI	ADJ	YES	ASSIGNEE	07-02-2008
Macrocyclon or Tyloxapol or Superinone or Alevaire or Tyloxypal or Superiuone or Enuclene or Exosurf or (Triton A-20) or (Triton WR 1339) or (Triton WR-1339) or "Triton W.R.1339" or Tiloxapol or Tyloxapolum or AIDS094886 or (AIDS-094886) or (NSC 90255) or (p-Isooctylpolyoxyethylenephenol formaldehyde polymer) or (Oxyethylated tertiary octyl-phenol-formaldehyde polymer) or (25301-02-4) or (Phenol, p-(1,1,3,3-tetramethylbutyl)-, polymer with ethylene oxide and formaldehyde) or (4-(1,1,3,3-Tetramethylbutyl)phenol, polymer with formaldehyde & oxirane) or (Formaldehyde, polymer with oxirane and 4-(1,1,3,3-tetra methylbutyl)phenol)	PGPB, USPT, USOC, EPAB, JPAB, DWPI	ADJ	YES	ASSIGNEE	07-02-2008

or (Formaldehyde, polymer with oxirane and 4-(1,1,3,3-tetramethylbutyl)phenol) or (p-(1,1,3,3-Tetramethylbutyl)phenol polymer with ethylene oxide and formaldehyde) or (Phenol, 4-(1,1,3,3-tetramethylbutyl)-, polymer with formaldehyde and oxirane)					
(Macrocyclon or Tyloxapol or Superinone or Alevaire or Tyloxypal or Superiuone or Enuclene or Exosurf or (Triton A-20) or (Triton WR 1339) or (Triton WR-1339) or "Triton W.R.1339" or Tiloxapol or Tyloxapolum or AIDS094886 or (AIDS-094886) or (NSC 90255) or (p-Isooctylpolyoxyethylenephenol formaldehyde polymer) or (Oxyethylated tertiary octyl-phenol-formaldehyde polymer) or (25301-02-4) or (Phenol, p-(1,1,3,3-tetramethylbutyl)-, polymer with ethylene oxide and formaldehyde) or (4-(1,1,3,3-Tetramethylbutyl)phenol, polymer with formaldehyde & oxirane) or (Formaldehyde, polymer with oxirane and 4-(1,1,3,3-tetra methylbutyl)phenol) or (Formaldehyde, polymer with oxirane and 4-(1,1,3,3-tetramethylbutyl)phenol) or (p-(1,1,3,3-Tetramethylbutyl)phenol polymer with ethylene oxide and formaldehyde) or (Phenol, 4-(1,1,3,3-tetramethylbutyl)-, polymer with formaldehyde and oxirane)) and (Bromfenac or Duract or (BROMFENAC SODIUM) or (AHR 10282B) or (Bromfenac monosodium salt sesquihydrate) or (Sodium (2-amino-3-(p-bromobenzoyl)phenyl)acetate sesquihydrate) or (Benzeneacetic acid, 2-amino-3-(4-bromobenzoyl)-, monosodium salt, hydrate (2:3)) or (Benzeneacetic acid, 2-amino-3-(4-bromobenzoyl)-, monosodium salt, sesquihydrate) or (120638-55-3) or (sodium 2-(2-amino-3-(4-bromobenzoyl)phenyl)acetate))	PGPB, USPT, USOC, EPAB, JPAB, DWPI	ADJ	YES	ASSIGNEE	07-02-2008
(Macrocyclon or Tyloxapol or Superinone or Alevaire or Tyloxypal or Superiuone or Enuclene or Exosurf or (Triton A-20) or (Triton WR 1339) or (Triton WR-1339) or "Triton W.R.1339" or Tiloxapol or Tyloxapolum or AIDS094886 or (AIDS-094886) or (NSC 90255) or (p-Isooctylpolyoxyethylenephenol formaldehyde polymer) or (Oxyethylated tertiary octyl-phenol-formaldehyde polymer) or (25301-02-4) or (Phenol, p-(1,1,3,3-tetramethylbutyl)-, polymer with ethylene oxide and formaldehyde) or (4-(1,1,3,3-Tetramethylbutyl)phenol, polymer with formaldehyde & oxirane) or (Formaldehyde, polymer with oxirane and 4-(1,1,3,3-tetra methylbutyl)phenol) or (Formaldehyde, polymer with oxirane and	PGPB, USPT, USOC, EPAB, JPAB, DWPI	ADJ	YES	ASSIGNEE	07-02-2008

4-(1,1,3,3-tetramethylbutyl)phenol) or (p-(1,1,3,3-Tetramethylbutyl)phenol polymer with ethylene oxide and formaldehyde) or (Phenol, 4-(1,1,3,3-tetramethylbutyl)-, polymer with formaldehyde and oxirane) and Bromfenac or Duract or (BROMFENAC SODIUM) or (AHR 10282B) or (Bromfenac monosodium salt sesquihydrate) or (Sodium (2-amino-3-(p-bromobenzoyl)phenyl)acetate sesquihydrate) or (Benzeneacetic acid, 2-amino-3-(4-bromobenzoyl)-, monosodium salt, hydrate (2:3)) or (Benzeneacetic acid, 2-amino-3-(4-bromobenzoyl)-, monosodium salt, sesquihydrate) or (120638-55-3) or (sodium 2-(2-amino-3-(4-bromobenzoyl)phenyl)acetate)) and (@pd<20030121 or @ad<20030121 or @rlad<20030121)					
(Macrocyclon or Tyloxapol or Superinone or Alevaire or Tyloxypal or Superiuone or Enuclene or Exosurf or (Triton A-20) or (Triton WR 1339) or (Triton WR-1339) or "Triton W.R.1339" or Tiloxapol or Tyloxapolum or AIDS094886 or (AIDS-094886) or (NSC 90255) or (p-Isooctylpolyoxyethylenephenol formaldehyde polymer) or (Oxyethylated tertiary octyl-phenol-formaldehyde polymer) or (25301-02-4) or (Phenol, p-(1,1,3,3-tetramethylbutyl)-, polymer with ethylene oxide and formaldehyde) or (4-(1,1,3,3-Tetramethylbutyl)phenol, polymer with formaldehyde & oxirane) or (Formaldehyde, polymer with oxirane and 4-(1,1,3,3-tetra methylbutyl)phenol) or (Formaldehyde, polymer with oxirane and 4-(1,1,3,3-tetramethylbutyl)phenol) or (p-(1,1,3,3-Tetramethylbutyl)phenol polymer with ethylene oxide and formaldehyde) or (Phenol, 4-(1,1,3,3-tetramethylbutyl)-, polymer with formaldehyde and oxirane) and Bromfenac or Duract or (BROMFENAC SODIUM) or (AHR 10282B) or (Bromfenac monosodium salt sesquihydrate) or (Sodium (2-amino-3-(p-bromobenzoyl)phenyl)acetate sesquihydrate) or (Benzeneacetic acid, 2-amino-3-(4-bromobenzoyl)-, monosodium salt, hydrate (2:3)) or (Benzeneacetic acid, 2-amino-3-(4-bromobenzoyl)-, monosodium salt, sesquihydrate) or (120638-55-3) or (sodium 2-(2-amino-3-(4-bromobenzoyl)phenyl)acetate) and (@pd<20030121 or @ad<20030121 or @rlad<20030121)) and ((Bromfenac or Duract or (BROMFENAC SODIUM) or (AHR 10282B) or (Bromfenac monosodium salt sesquihydrate) or (Sodium (2-amino-3-(p-bromobenzoyl)phenyl)acetate sesquihydrate) or (Benzeneacetic acid,	PGPB, USPT, USOC, EPAB, JPAB, DWPI	ADJ	YES	ASSIGNEE	07-02-2008

2-amino-3-(4-bromobenzoyl)-, monosodium salt, hydrate (2:3)) or (Benzeneacetic acid, 2-amino-3-(4-bromobenzoyl)-, monosodium salt, sesquihydrate) or (120638-55-3) or (sodium 2-(2-amino-3-(4-bromobenzoyl)phenyl)acetate)) or (Macrocyclon or Tyloxapol or Superinone or Alevaire or Tyloxypal or Superiuone or Enuclene or Exosurf or (Triton A-20) or (Triton WR 1339) or (Triton WR-1339) or "Triton W.R.1339" or Tiloxapol or Tyloxapolum or AIDS094886 or (AIDS-094886) or (NSC 90255) or (p-Isooctylpolyoxyethylenephenol formaldehyde polymer) or (Oxyethylated tertiary octyl-phenol-formaldehyde polymer) or (25301-02-4) or (Phenol, p-(1,1,3,3-tetramethylbutyl)-, polymer with ethylene oxide and formaldehyde) or (4-(1,1,3,3-Tetramethylbutyl)phenol, polymer with formaldehyde & oxirane) or (Formaldehyde, polymer with oxirane and 4-(1,1,3,3-tetra methylbutyl)phenol) or (Formaldehyde, polymer with oxirane and 4-(1,1,3,3-tetramethylbutyl)phenol) or (p-(1,1,3,3-Tetramethylbutyl)phenol polymer with ethylene oxide and formaldehyde) or (Phenol, 4-(1,1,3,3-tetramethylbutyl)-, polymer with formaldehyde and oxirane))).ti,ab.					
(Macrocyclon or Tyloxapol or Superinone or Alevaire or Tyloxypal or Superiuone or Enuclene or Exosurf or (Triton A-20) or (Triton WR 1339) or (Triton WR-1339) or "Triton W.R.1339" or Tiloxapol or Tyloxapolum or AIDS094886 or (AIDS-094886) or (NSC 90255) or (p-Isooctylpolyoxyethylenephenol formaldehyde polymer) or (Oxyethylated tertiary octyl-phenol-formaldehyde polymer) or (25301-02-4) or (Phenol, p-(1,1,3,3-tetramethylbutyl)-, polymer with ethylene oxide and formaldehyde) or (4-(1,1,3,3-Tetramethylbutyl)phenol, polymer with formaldehyde & oxirane) or (Formaldehyde, polymer with oxirane and 4-(1,1,3,3-tetra methylbutyl)phenol) or (Formaldehyde, polymer with oxirane and 4-(1,1,3,3-tetramethylbutyl)phenol) or (p-(1,1,3,3-Tetramethylbutyl)phenol polymer with ethylene oxide and formaldehyde) or (Phenol, 4-(1,1,3,3-tetramethylbutyl)-, polymer with formaldehyde and oxirane) and Bromfenac or Duract or (BROMFENAC SODIUM) or (AHR 10282B) or (Bromfenac monosodium salt sesquihydrate) or (Sodium (2-amino-3-(p-bromobenzoyl)phenyl)acetate sesquihydrate) or (Benzeneacetic acid, 2-amino-3-(4-bromobenzoyl)-, monosodium salt, hydrate (2:3)) or (Benzeneacetic acid, 2-amino-3-(4-bromobenzoyl)-, monosodium salt,	PGPB, USPT, USOC, EPAB, JPAB, DWPI	ADJ	YES	ASSIGNEE	07-02-2008

sesquihydrate) or (120638-55-3) or (sodium 2-(2-amino-3-(4-bromobenzoyl)phenyl)acetate) and (@pd<20030121 or @ad<20030121 or @rlad<20030121)) and ((Bromfenac or Duract or (BROMFENAC SODIUM) or (AHR 10282B) or (Bromfenac monosodium salt sesquihydrate) or (Sodium (2-amino-3-(p-bromobenzoyl)phenyl)acetate sesquihydrate) or (Benzeneacetic acid, 2-amino-3-(4-bromobenzoyl)-, monosodium salt, hydrate (2:3)) or (Benzeneacetic acid, 2-amino-3-(4-bromobenzoyl)-, monosodium salt, sesquihydrate) or (120638-55-3) or (sodium 2-(2-amino-3-(4-bromobenzoyl)phenyl)acetate)) .ti,ab. or (Macrocyclon or Tyloxapol or Superinone or Alevaire or Tyloxypal or Superiuone or Enuclene or Exosurf or (Triton A-20) or (Triton WR 1339) or (Triton WR-1339) or "Triton W.R.1339" or Tiloxapol or Tyloxapolum or AIDS094886 or (AIDS-094886) or (NSC 90255) or (p-Isooctylpolyoxyethylenephenol formaldehyde polymer) or (Oxyethylated tertiary octyl-phenol-formaldehyde polymer) or (25301-02-4) or (Phenol, p-(1,1,3,3-tetramethylbutyl)-, polymer with ethylene oxide and formaldehyde) or (4-(1,1,3,3-Tetramethylbutyl)phenol, polymer with formaldehyde & oxirane) or (Formaldehyde, polymer with oxirane and 4-(1,1,3,3-tetra methylbutyl)phenol) or (Formaldehyde, polymer with oxirane and 4-(1,1,3,3-tetramethylbutyl)phenol) or (p-(1,1,3,3-Tetramethylbutyl)phenol polymer with ethylene oxide and formaldehyde) or (Phenol, 4-(1,1,3,3-tetramethylbutyl)-, polymer with formaldehyde and oxirane)) .ti,ab.)					
((Bromfenac or Duract or (BROMFENAC SODIUM) or (AHR 10282B) or (Bromfenac monosodium salt sesquihydrate) or (Sodium (2-amino-3-(p-bromobenzoyl)phenyl)acetate sesquihydrate) or (Benzeneacetic acid, 2-amino-3-(4-bromobenzoyl)-, monosodium salt, hydrate (2:3)) or (Benzeneacetic acid, 2-amino-3-(4-bromobenzoyl)-, monosodium salt, sesquihydrate) or (120638-55-3) or (sodium 2-(2-amino-3-(4-bromobenzoyl)phenyl)acetate)) .ti,ab. or (Macrocyclon or Tyloxapol or Superinone or Alevaire or Tyloxypal or Superiuone or Enuclene or Exosurf or (Triton A-20) or (Triton WR 1339) or (Triton WR-1339) or "Triton W.R.1339" or Tiloxapol or Tyloxapolum or AIDS094886 or (AIDS-094886) or (NSC 90255) or (p-Isooctylpolyoxyethylenephenol formaldehyde polymer) or (Oxyethylated tertiary octyl-phenol-formaldehyde polymer) or (25301-02-4)	PGPB, USPT, USOC, EPAB, JPAB, DWPI	ADJ	YES	ASSIGNEE	07-02-2008

or (Phenol, p-(1,1,3,3-tetramethylbutyl)-, polymer with ethylene oxide and formaldehyde) or (4-(1,1,3,3-Tetramethylbutyl)phenol, polymer with formaldehyde & oxirane) or (Formaldehyde, polymer with oxirane and 4-(1,1,3,3-tetra methylbutyl)phenol) or (Formaldehyde, polymer with oxirane and 4-(1,1,3,3-tetramethylbutyl)phenol) or (p-(1,1,3,3-Tetramethylbutyl)phenol polymer with ethylene oxide and formaldehyde) or (Phenol, 4-(1,1,3,3-tetramethylbutyl)-, polymer with formaldehyde and oxirane)) .ti,ab.)					
(Bromfenac or Duract or (BROMFENAC SODIUM) or (AHR 10282B) or (Bromfenac monosodium salt sesquihydrate) or (Sodium (2-amino-3-(p-bromobenzoyl)phenyl)acetate sesquihydrate) or (Benzeneacetic acid, 2-amino-3-(4-bromobenzoyl)-, monosodium salt, hydrate (2:3)) or (Benzeneacetic acid, 2-amino-3-(4-bromobenzoyl)-, monosodium salt, sesquihydrate) or (120638-55-3) or (sodium 2-(2-amino-3-(4-bromobenzoyl)phenyl)acetate)) .ti,ab,clm. or (Macrocyclon or Tyloxapol or Superinone or Alevaire or Tyloxypal or Superiuone or Enuclene or Exosurf or (Triton A-20) or (Triton WR 1339) or (Triton WR-1339) or "Triton W.R.1339" or Tiloxapol or Tyloxapolum or AIDS094886 or (AIDS-094886) or (NSC 90255) or (p-Isooctylpolyoxyethylenephenol formaldehyde polymer) or (Oxyethylated tertiary octyl-phenol-formaldehyde polymer) or (25301-02-4) or (Phenol, p-(1,1,3,3-tetramethylbutyl)-, polymer with ethylene oxide and formaldehyde) or (4-(1,1,3,3-Tetramethylbutyl)phenol, polymer with formaldehyde & oxirane) or (Formaldehyde, polymer with oxirane and 4-(1,1,3,3-tetra methylbutyl)phenol) or (Formaldehyde, polymer with oxirane and 4-(1,1,3,3-tetramethylbutyl)phenol) or (p-(1,1,3,3-Tetramethylbutyl)phenol polymer with ethylene oxide and formaldehyde) or (Phenol, 4-(1,1,3,3-tetramethylbutyl)-, polymer with formaldehyde and oxirane)) .ti,ab,clm.	PGPB, USPT, USOC, EPAB, JPAB, DWPI	ADJ	YES	ASSIGNEE	07-02-2008
((Bromfenac or Duract or (BROMFENAC SODIUM) or (AHR 10282B) or (Bromfenac monosodium salt sesquihydrate) or (Sodium (2-amino-3-(p-bromobenzoyl)phenyl)acetate sesquihydrate) or (Benzeneacetic acid, 2-amino-3-(4-bromobenzoyl)-, monosodium salt, hydrate (2:3)) or (Benzeneacetic acid, 2-amino-3-(4-bromobenzoyl)-, monosodium salt,	PGPB, USPT, USOC, EPAB, JPAB, DWPI	ADJ	YES	ASSIGNEE	07-02-2008

sesquihydrate) or (120638-55-3) or (sodium 2-(2-amino-3-(4-bromobenzoyl)phenyl)acetate)) or (Macrocyclon or Tyloxapol or Superinone or Alevaire or Tyloxypal or Superiuone or Enuclene or Exosurf or (Triton A-20) or (Triton WR 1339) or (Triton WR-1339) or "Triton W.R.1339" or Tiloxapol or Tyloxapolum or AIDS094886 or (AIDS-094886) or (NSC 90255) or (p-Isooctylpolyoxyethylenephenol formaldehyde polymer) or (Oxyethylated tertiary octyl-phenol-formaldehyde polymer) or (25301-02-4) or (Phenol, p-(1,1,3,3-tetramethylbutyl)-, polymer with ethylene oxide and formaldehyde) or (4-(1,1,3,3-Tetramethylbutyl)phenol, polymer with formaldehyde & oxirane) or (Formaldehyde, polymer with oxirane and 4-(1,1,3,3-tetra methylbutyl)phenol) or (Formaldehyde, polymer with oxirane and 4-(1,1,3,3-tetramethylbutyl)phenol) or (p-(1,1,3,3-Tetramethylbutyl)phenol polymer with ethylene oxide and formaldehyde) or (Phenol, 4-(1,1,3,3-tetramethylbutyl)-, polymer with formaldehyde and oxirane))).ti,ab,clm.					
(Bromfenac or Duract or (BROMFENAC SODIUM) or (AHR 10282B) or (Bromfenac monosodium salt sesquihydrate) or (Sodium (2-amino-3-(p-bromobenzoyl)phenyl)acetate sesquihydrate) or (Benzeneacetic acid, 2-amino-3-(4-bromobenzoyl)-, monosodium salt, hydrate (2:3)) or (Benzeneacetic acid, 2-amino-3-(4-bromobenzoyl)-, monosodium salt, sesquihydrate) or (120638-55-3) or (sodium 2-(2-amino-3-(4-bromobenzoyl)phenyl)acetate)) .ti,ab,clm.	PGPB, USPT, USOC, EPAB, JPAB, DWPI	ADJ	YES	ASSIGNEE	07-02-2008
(Macrocyclon or Tyloxapol or Superinone or Alevaire or Tyloxypal or Superiuone or Enuclene or Exosurf or (Triton A-20) or (Triton WR 1339) or (Triton WR-1339) or "Triton W.R.1339" or Tiloxapol or Tyloxapolum or AIDS094886 or (AIDS-094886) or (NSC 90255) or (p-Isooctylpolyoxyethylenephenol formaldehyde polymer) or (Oxyethylated tertiary octyl-phenol-formaldehyde polymer) or (25301-02-4) or (Phenol, p-(1,1,3,3-tetramethylbutyl)-, polymer with ethylene oxide and formaldehyde) or (4-(1,1,3,3-Tetramethylbutyl)phenol, polymer with formaldehyde & oxirane) or (Formaldehyde, polymer with oxirane and 4-(1,1,3,3-tetra methylbutyl)phenol) or (Formaldehyde, polymer with oxirane and 4-(1,1,3,3-tetramethylbutyl)phenol) or (p-(1,1,3,3-Tetramethylbutyl)phenol polymer with ethylene oxide and formaldehyde) or (Phenol,	PGPB, USPT, USOC, EPAB, JPAB, DWPI	ADJ	YES	ASSIGNEE	07-02-2008

4-(1,1,3,3-tetramethylbutyl)-, polymer with formaldehyde and oxirane)) .ti,ab,clm.					
(Macrocyclon or Tyloxapol or Superinone or Alevaire or Tyloxypal or Superiuone or Enuclene or Exosurf or (Triton A-20) or (Triton WR 1339) or (Triton WR-1339) or "Triton W.R.1339" or Tiloxapol or Tyloxapolum or AIDS094886 or (AIDS-094886) or (NSC 90255) or (p-Isooctylpolyoxyethylenephenol formaldehyde polymer) or (Oxyethylated tertiary octyl-phenol-formaldehyde polymer) or (25301-02-4) or (Phenol, p-(1,1,3,3-tetramethylbutyl)-, polymer with ethylene oxide and formaldehyde) or (4-(1,1,3,3-Tetramethylbutyl)phenol, polymer with formaldehyde & oxirane) or (Formaldehyde, polymer with oxirane and 4-(1,1,3,3-tetra methylbutyl)phenol) or (Formaldehyde, polymer with oxirane and 4-(1,1,3,3-tetramethylbutyl)phenol) or (p-(1,1,3,3-Tetramethylbutyl)phenol polymer with ethylene oxide and formaldehyde) or (Phenol, 4-(1,1,3,3-tetramethylbutyl)-, polymer with formaldehyde and oxirane)) .ti,ab,clm.	PGPB, USPT, USOC, EPAB, JPAB, DWPI	ADJ	YES	ASSIGNEE	07-02-2008
(Macrocyclon or Tyloxapol or Superinone or Alevaire or Tyloxypal or Superiuone or Enuclene or Exosurf or (Triton A-20) or (Triton WR 1339) or (Triton WR-1339) or "Triton W.R.1339" or Tiloxapol or Tyloxapolum or AIDS094886 or (AIDS-094886) or (NSC 90255) or (p-Isooctylpolyoxyethylenephenol formaldehyde polymer) or (Oxyethylated tertiary octyl-phenol-formaldehyde polymer) or (25301-02-4) or (Phenol, p-(1,1,3,3-tetramethylbutyl)-, polymer with ethylene oxide and formaldehyde) or (4-(1,1,3,3-Tetramethylbutyl)phenol, polymer with formaldehyde & oxirane) or (Formaldehyde, polymer with oxirane and 4-(1,1,3,3-tetra methylbutyl)phenol) or (Formaldehyde, polymer with oxirane and 4-(1,1,3,3-tetramethylbutyl)phenol) or (p-(1,1,3,3-Tetramethylbutyl)phenol polymer with ethylene oxide and formaldehyde) or (Phenol, 4-(1,1,3,3-tetramethylbutyl)-, polymer with formaldehyde and oxirane)) .ti,ab,clm.	PGPB, USPT, USOC, EPAB, JPAB, DWPI	ADJ	YES	ASSIGNEE	07-02-2008
(Macrocyclon or Tyloxapol or Superinone or Alevaire or Tyloxypal or Superiuone or Enuclene or Exosurf or (Triton A-20) or (Triton WR 1339) or (Triton WR-1339) or "Triton W.R.1339" or Tiloxapol or Tyloxapolum or AIDS094886 or (AIDS-094886) or (NSC 90255) or (p-Isooctylpolyoxyethylenephenol formaldehyde polymer) or (Oxyethylated tertiary octyl-phenol-formaldehyde polymer) or (25301-02-4) or (Phenol, p-(1,1,3,3-tetramethylbutyl)-, polymer	PGPB, USPT, USOC, EPAB, JPAB, DWPI	ADJ	YES	ASSIGNEE	07-02-2008

with ethylene oxide and formaldehyde) or (4-(1,1,3,3-Tetramethylbutyl)phenol, polymer with formaldehyde & oxirane) or (Formaldehyde, polymer with oxirane and 4-(1,1,3,3-tetra methylbutyl)phenol) or (Formaldehyde, polymer with oxirane and 4-(1,1,3,3-tetramethylbutyl)phenol) or (p-(1,1,3,3-Tetramethylbutyl)phenol polymer with ethylene oxide and formaldehyde) or (Phenol, 4-(1,1,3,3-tetramethylbutyl)-, polymer with formaldehyde and oxirane)) .ti. or (Macrocyclon or Tyloxapol or Superinone or Alevaire or Tyloxypal or Superiuone or Enuclene or Exosurf or (Triton A-20) or (Triton WR 1339) or (Triton WR-1339) or "Triton W.R.1339" or Tiloxapol or Tyloxapolum or AIDS094886 or (AIDS-094886) or (NSC 90255) or (p-Isooctylpolyoxyethylenephenol formaldehyde polymer) or (Oxyethylated tertiary octyl-phenol-formaldehyde polymer) or (25301-02-4) or (Phenol, p-(1,1,3,3-tetramethylbutyl)-, polymer with ethylene oxide and formaldehyde) or (4-(1,1,3,3-Tetramethylbutyl)phenol, polymer with formaldehyde & oxirane) or (Formaldehyde, polymer with oxirane and 4-(1,1,3,3-tetra methylbutyl)phenol) or (Formaldehyde, polymer with oxirane and 4-(1,1,3,3-tetramethylbutyl)phenol) or (p-(1,1,3,3-Tetramethylbutyl)phenol polymer with ethylene oxide and formaldehyde) or (Phenol, 4-(1,1,3,3-tetramethylbutyl)-, polymer with formaldehyde and oxirane)) .ab. or (Macrocyclon or Tyloxapol or Superinone or Alevaire or Tyloxypal or Superiuone or Enuclene or Exosurf or (Triton A-20) or (Triton WR 1339) or (Triton WR-1339) or "Triton W.R.1339" or Tiloxapol or Tyloxapolum or AIDS094886 or (AIDS-094886) or (NSC 90255) or (p-Isooctylpolyoxyethylenephenol formaldehyde polymer) or (Oxyethylated tertiary octyl-phenol-formaldehyde polymer) or (25301-02-4) or (Phenol, p-(1,1,3,3-tetramethylbutyl)-, polymer with ethylene oxide and formaldehyde) or (4-(1,1,3,3-Tetramethylbutyl)phenol, polymer with formaldehyde & oxirane) or (Formaldehyde, polymer with oxirane and 4-(1,1,3,3-tetra methylbutyl)phenol) or (Formaldehyde, polymer with oxirane and 4-(1,1,3,3-tetramethylbutyl)phenol) or (p-(1,1,3,3-Tetramethylbutyl)phenol polymer with ethylene oxide and formaldehyde) or (Phenol, 4-(1,1,3,3-tetramethylbutyl)-, polymer with formaldehyde and oxirane)) .clm.					
tyloxapol.ti,ab,clm.	PGPB, USPT,	ADJ	YES	ASSIGNEE	07-02-2008

	USOC, EPAB, JPAB, DWPI				
(Macrocyclon or Tyloxapol or Superinone or Alevaire or Tyloxypal or Superiuone or Enuclene or Exosurf or (Triton A-20) or (Triton WR 1339) or (Triton WR-1339) or "Triton W.R.1339" or Tiloxapol or Tyloxapolum or AIDS094886 or (AIDS-094886) or (NSC 90255) or (p-Isooctylpolyoxyethylenephenol formaldehyde polymer) or (Oxyethylated tertiary octyl-phenol-formaldehyde polymer) or (25301-02-4) or (Phenol, p-(1,1,3,3-tetramethylbutyl)-, polymer with ethylene oxide and formaldehyde) or (4-(1,1,3,3-Tetramethylbutyl)phenol, polymer with formaldehyde & oxirane) or (Formaldehyde, polymer with oxirane and 4-(1,1,3,3-tetra methylbutyl)phenol) or (Formaldehyde, polymer with oxirane and 4-(1,1,3,3-tetramethylbutyl)phenol) or (p-(1,1,3,3-Tetramethylbutyl)phenol polymer with ethylene oxide and formaldehyde) or (Phenol, 4-(1,1,3,3-tetramethylbutyl)-, polymer with formaldehyde and oxirane) and Bromfenac or Duract or (BROMFENAC SODIUM) or (AHR 10282B) or (Bromfenac monosodium salt sesquihydrate) or (Sodium (2-amino-3-(p-bromobenzoyl)phenyl)acetate sesquihydrate) or (Benzeneacetic acid, 2-amino-3-(4-bromobenzoyl)-, monosodium salt, hydrate (2:3)) or (Benzeneacetic acid, 2-amino-3-(4-bromobenzoyl)-, monosodium salt, sesquihydrate) or (120638-55-3) or (sodium 2-(2-amino-3-(4-bromobenzoyl)phenyl)acetate) and (@pd<20030121 or @ad<20030121 or @rlad<20030121)) and ((Bromfenac or Duract or (BROMFENAC SODIUM) or (AHR 10282B) or (Bromfenac monosodium salt sesquihydrate) or (Sodium (2-amino-3-(p-bromobenzoyl)phenyl)acetate sesquihydrate) or (Benzeneacetic acid, 2-amino-3-(4-bromobenzoyl)-, monosodium salt, hydrate (2:3)) or (Benzeneacetic acid, 2-amino-3-(4-bromobenzoyl)-, monosodium salt, sesquihydrate) or (120638-55-3) or (sodium 2-(2-amino-3-(4-bromobenzoyl)phenyl)acetate) .ti,ab,clm.) or (tyloxapol.ti,ab,clm.))	PGPB, USPT, USOC, EPAB, JPAB, DWPI	ADJ	YES	ASSIGNEE	07-02-2008
(Bromfenac or Duract or (BROMFENAC SODIUM) or (AHR 10282B) or (Bromfenac monosodium salt sesquihydrate) or (Sodium (2-amino-3-(p-bromobenzoyl)phenyl)acetate sesquihydrate) or (Benzeneacetic acid,	PGPB, USPT, USOC, EPAB, JPAB,	ADJ	YES	ASSIGNEE	07-03-2008

2-amino-3-(4-bromobenzoyl)-, monosodium salt, hydrate (2:3)) or (Benzeneacetic acid, 2-amino-3-(4-bromobenzoyl)-, monosodium salt, sesquihydrate) or (120638-55-3) or (sodium 2-(2-amino-3-(4-bromobenzoyl)phenyl)acetate))	DWPI				
(Macrocyclon or Tyloxapol or Superinone or Alevaire or Tyloxypal or Superiuone or Enuclene or Exosurf or (Triton A-20) or (Triton WR 1339) or (Triton WR-1339 Triton W.R.1339) or Tiloxapol or Tyloxapolum or AIDS094886 or (AIDS-094886) or (NSC 90255) or (p-Isooctylpolyoxyethylenephenol formaldehyde polymer) or (Oxyethylated tertiary octyl-phenol-formaldehyde polymer) or (25301-02-4) or (Phenol, p-(1,1,3,3-tetramethylbutyl)-, polymer with ethylene oxide and formaldehyde) or (4-(1,1,3,3-Tetramethylbutyl)phenol, polymer with formaldehyde & oxirane) or (Formaldehyde, polymer with oxirane and 4-(1,1,3,3-tetra methylbutyl)phenol) or (Formaldehyde, polymer with oxirane and 4-(1,1,3,3-tetramethylbutyl)phenol) or (p-(1,1,3,3-Tetramethylbutyl)phenol polymer with ethylene oxide and formaldehyde) or (Phenol, 4-(1,1,3,3-tetramethylbutyl)-, polymer with formaldehyde and oxirane))	PGPB, USPT, USOC, EPAB, JPAB, DWPI	ADJ	YES	ASSIGNEE	07-03-2008
(Bromfenac or Duract or (BROMFENAC SODIUM) or (AHR 10282B) or (Bromfenac monosodium salt sesquihydrate) or (Sodium (2-amino-3-(p-bromobenzoyl)phenyl)acetate sesquihydrate) or (Benzeneacetic acid, 2-amino-3-(4-bromobenzoyl)-, monosodium salt, hydrate (2:3)) or (Benzeneacetic acid, 2-amino-3-(4-bromobenzoyl)-, monosodium salt, sesquihydrate) or (120638-55-3) or (sodium 2-(2-amino-3-(4-bromobenzoyl)phenyl)acetate))	PGPB, USPT, USOC, EPAB, JPAB, DWPI	ADJ	YES	ASSIGNEE	07-03-2008
(Macrocyclon or Tyloxapol or Superinone or Alevaire or Tyloxypal or Superiuone or Enuclene or Exosurf or (Triton A-20) or (Triton WR 1339) or (Triton WR-1339) or "Triton W.R.1339" or Tiloxapol or Tyloxapolum or AIDS094886 or (AIDS-094886) or (NSC 90255) or (p-Isooctylpolyoxyethylenephenol formaldehyde polymer) or (Oxyethylated tertiary octyl-phenol-formaldehyde polymer) or (25301-02-4) or (Phenol, p-(1,1,3,3-tetramethylbutyl)-, polymer with ethylene oxide and formaldehyde) or (4-(1,1,3,3-Tetramethylbutyl)phenol, polymer with formaldehyde & oxirane) or (Formaldehyde, polymer with oxirane and 4-(1,1,3,3-tetra methylbutyl)phenol) or (Formaldehyde, polymer with oxirane and 4-(1,1,3,3-tetramethylbutyl)phenol) or	PGPB, USPT, USOC, EPAB, JPAB, DWPI	ADJ	YES	ASSIGNEE	07-03-2008

(p-(1,1,3,3-Tetramethylbutyl)phenol polymer with ethylene oxide and formaldehyde) or (Phenol, 4-(1,1,3,3-tetramethylbutyl)-, polymer with formaldehyde and oxirane))					
((Bromfenac or Duract or (BROMFENAC SODIUM) or (AHR 10282B) or (Bromfenac monosodium salt sesquihydrate) or (Sodium (2-amino-3-(p-bromobenzoyl)phenyl)acetate sesquihydrate) or (Benzeneacetic acid, 2-amino-3-(4-bromobenzoyl)-, monosodium salt, hydrate (2:3)) or (Benzeneacetic acid, 2-amino-3-(4-bromobenzoyl)-, monosodium salt, sesquihydrate) or (120638-55-3) or (sodium 2-(2-amino-3-(4-bromobenzoyl)phenyl)acetate))) and ((Macrocyclon or Tyloxapol or Superinone or Alevaire or Tyloxypal or Superiuone or Enuclene or Exosurf or (Triton A-20) or (Triton WR 1339) or (Triton WR-1339) or "Triton W.R.1339" or Tiloxapol or Tyloxapolum or AIDS094886 or (AIDS-094886) or (NSC 90255) or (p-Isooctylpolyoxyethylenephenol formaldehyde polymer) or (Oxyethylated tertiary octyl-phenol-formaldehyde polymer) or (25301-02-4) or (Phenol, p-(1,1,3,3-tetramethylbutyl)-, polymer with ethylene oxide and formaldehyde) or (4-(1,1,3,3-Tetramethylbutyl)phenol, polymer with formaldehyde & oxirane) or (Formaldehyde, polymer with oxirane and 4-(1,1,3,3-tetra methylbutyl)phenol) or (Formaldehyde, polymer with oxirane and 4-(1,1,3,3-tetramethylbutyl)phenol) or (p-(1,1,3,3-Tetramethylbutyl)phenol polymer with ethylene oxide and formaldehyde) or (Phenol, 4-(1,1,3,3-tetramethylbutyl)-, polymer with formaldehyde and oxirane)))	PGPB, USPT, USOC, EPAB, JPAB, DWPI	ADJ	YES	ASSIGNEE	07-03-2008
((Bromfenac or Duract or (BROMFENAC SODIUM) or (AHR 10282B) or (Bromfenac monosodium salt sesquihydrate) or (Sodium (2-amino-3-(p-bromobenzoyl)phenyl)acetate sesquihydrate) or (Benzeneacetic acid, 2-amino-3-(4-bromobenzoyl)-, monosodium salt, hydrate (2:3)) or (Benzeneacetic acid, 2-amino-3-(4-bromobenzoyl)-, monosodium salt, sesquihydrate) or (120638-55-3) or (sodium 2-(2-amino-3-(4-bromobenzoyl)phenyl)acetate)) and (Macrocyclon or Tyloxapol or Superinone or Alevaire or Tyloxypal or Superiuone or Enuclene or Exosurf or (Triton A-20) or (Triton WR 1339) or (Triton WR-1339) or "Triton W.R.1339" or Tiloxapol or Tyloxapolum or AIDS094886 or (AIDS-094886) or (NSC 90255) or (p-Isooctylpolyoxyethylenephenol	PGPB, USPT, USOC, EPAB, JPAB, DWPI	ADJ	YES	ASSIGNEE	07-03-2008

formaldehyde polymer) or (Oxyethylated tertiary octyl-phenol-formaldehyde polymer) or (25301-02-4) or (Phenol, p-(1,1,3,3-tetramethylbutyl)-, polymer with ethylene oxide and formaldehyde) or (4-(1,1,3,3-Tetramethylbutyl)phenol, polymer with formaldehyde & oxirane) or (Formaldehyde, polymer with oxirane and 4-(1,1,3,3-tetra methylbutyl)phenol) or (Formaldehyde, polymer with oxirane and 4-(1,1,3,3-tetramethylbutyl)phenol) or (p-(1,1,3,3-Tetramethylbutyl)phenol polymer with ethylene oxide and formaldehyde) or (Phenol, 4-(1,1,3,3-tetramethylbutyl)-, polymer with formaldehyde and oxirane))) and (@pd<20030121 or @ad<20030121 or @rlad<20030121)					
((Bromfenac or Duract or (BROMFENAC SODIUM) or (AHR 10282B) or (Bromfenac monosodium salt sesquihydrate) or (Sodium (2-amino-3-(p-bromobenzoyl)phenyl)acetate sesquihydrate) or (Benzeneacetic acid, 2-amino-3-(4-bromobenzoyl)-, monosodium salt, hydrate (2:3)) or (Benzeneacetic acid, 2-amino-3-(4-bromobenzoyl)-, monosodium salt, sesquihydrate) or (120638-55-3) or (sodium 2-(2-amino-3-(4-bromobenzoyl)phenyl)acetate)) and (Macrocyclon or Tyloxapol or Superinone or Alevaire or Tyloxypal or Superiuone or Enuclene or Exosurf or (Triton A-20) or (Triton WR 1339) or (Triton WR-1339) or "Triton W.R.1339" or Tiloxapol or Tyloxapolum or AIDS094886 or (AIDS-094886) or (NSC 90255) or (p-Isooctylpolyoxyethylenephenol formaldehyde polymer) or (Oxyethylated tertiary octyl-phenol-formaldehyde polymer) or (25301-02-4) or (Phenol, p-(1,1,3,3-tetramethylbutyl)-, polymer with ethylene oxide and formaldehyde) or (4-(1,1,3,3-Tetramethylbutyl)phenol, polymer with formaldehyde & oxirane) or (Formaldehyde, polymer with oxirane and 4-(1,1,3,3-tetra methylbutyl)phenol) or (Formaldehyde, polymer with oxirane and 4-(1,1,3,3-tetramethylbutyl)phenol) or (p-(1,1,3,3-Tetramethylbutyl)phenol polymer with ethylene oxide and formaldehyde) or (Phenol, 4-(1,1,3,3-tetramethylbutyl)-, polymer with formaldehyde and oxirane)) and (@pd<20030121 or @ad<20030121 or @rlad<20030121)) and (((Bromfenac or Duract or (BROMFENAC SODIUM) or (AHR 10282B) or (Bromfenac monosodium salt sesquihydrate) or (Sodium (2-amino-3-(p-bromobenzoyl)phenyl)acetate sesquihydrate) or (Benzeneacetic acid, 2-amino-3-(4-bromobenzoyl)-, monosodium salt,	PGPB, USPT, USOC, EPAB, JPAB, DWPI	ADJ	YES	ASSIGNEE	07-03-2008

hydrate (2:3)) or (Benzeneacetic acid, 2-amino-3-(4-bromobenzoyl)-, monosodium salt, sesquihydrate) or (120638-55-3) or (sodium 2-(2-amino-3-(4-bromobenzoyl)phenyl)acetate))) with ((Macrocyclon or Tyloxapol or Superinone or Alevaire or Tyloxypal or Superiuone or Enuclene or Exosurf or (Triton A-20) or (Triton WR 1339) or (Triton WR-1339) or "Triton W.R.1339" or Tiloxapol or Tyloxapolum or AIDS094886 or (AIDS-094886) or (NSC 90255) or (p-Isooctylpolyoxyethylenephenol formaldehyde polymer) or (Oxyethylated tertiary octyl-phenol-formaldehyde polymer) or (25301-02-4) or (Phenol, p-(1,1,3,3-tetramethylbutyl)-, polymer with ethylene oxide and formaldehyde) or (4-(1,1,3,3-Tetramethylbutyl)phenol, polymer with formaldehyde & oxirane) or (Formaldehyde, polymer with oxirane and 4-(1,1,3,3-tetra methylbutyl)phenol) or (Formaldehyde, polymer with oxirane and 4-(1,1,3,3-tetramethylbutyl)phenol) or (p-(1,1,3,3-Tetramethylbutyl)phenol polymer with ethylene oxide and formaldehyde) or (Phenol, 4-(1,1,3,3-tetramethylbutyl)-, polymer with formaldehyde and oxirane))))					
(((Bromfenac or Duract or (BROMFENAC SODIUM) or (AHR 10282B) or (Bromfenac monosodium salt sesquihydrate) or (Sodium (2-amino-3-(p-bromobenzoyl)phenyl)acetate sesquihydrate) or (Benzeneacetic acid, 2-amino-3-(4-bromobenzoyl)-, monosodium salt, hydrate (2:3)) or (Benzeneacetic acid, 2-amino-3-(4-bromobenzoyl)-, monosodium salt, sesquihydrate) or (120638-55-3) or (sodium 2-(2-amino-3-(4-bromobenzoyl)phenyl)acetate))) with ((Macrocyclon or Tyloxapol or Superinone or Alevaire or Tyloxypal or Superiuone or Enuclene or Exosurf or (Triton A-20) or (Triton WR 1339) or (Triton WR-1339) or "Triton W.R.1339" or Tiloxapol or Tyloxapolum or AIDS094886 or (AIDS-094886) or (NSC 90255) or (p-Isooctylpolyoxyethylenephenol formaldehyde polymer) or (Oxyethylated tertiary octyl-phenol-formaldehyde polymer) or (25301-02-4) or (Phenol, p-(1,1,3,3-tetramethylbutyl)-, polymer with ethylene oxide and formaldehyde) or (4-(1,1,3,3-Tetramethylbutyl)phenol, polymer with formaldehyde & oxirane) or (Formaldehyde, polymer with oxirane and 4-(1,1,3,3-tetra methylbutyl)phenol) or (Formaldehyde, polymer with oxirane and 4-(1,1,3,3-tetramethylbutyl)phenol) or (p-(1,1,3,3-Tetramethylbutyl)phenol polymer with ethylene oxide and formaldehyde) or (Phenol,	PGPB, USPT, USOC, EPAB, JPAB, DWPI	ADJ	YES	ASSIGNEE	07-03-2008

4-(1,1,3,3-tetramethylbutyl)-, polymer with formaldehyde and oxirane))))					
((Bromfenac or Duract or (BROMFENAC SODIUM) or (AHR 10282B) or (Bromfenac monosodium salt sesquihydrate) or (Sodium (2-amino-3-(p-bromobenzoyl)phenyl)acetate sesquihydrate) or (Benzeneacetic acid, 2-amino-3-(4-bromobenzoyl)-, monosodium salt, hydrate (2:3)) or (Benzeneacetic acid, 2-amino-3-(4-bromobenzoyl)-, monosodium salt, sesquihydrate) or (120638-55-3) or (sodium 2-(2-amino-3-(4-bromobenzoyl)phenyl)acetate))) with ((Macrocyclon or Tyloxapol or Superinone or Alevaire or Tyloxypal or Superiuone or Enuclene or Exosurf or (Triton A-20) or (Triton WR 1339) or (Triton WR-1339) or "Triton W.R.1339" or Tiloxapol or Tyloxapolum or AIDS094886 or (AIDS-094886) or (NSC 90255) or (p-Isooctylpolyoxyethylenephenol formaldehyde polymer) or (Oxyethylated tertiary octyl-phenol-formaldehyde polymer) or (25301-02-4) or (Phenol, p-(1,1,3,3-tetramethylbutyl)-, polymer with ethylene oxide and formaldehyde) or (4-(1,1,3,3-Tetramethylbutyl)phenol, polymer with formaldehyde & oxirane) or (Formaldehyde, polymer with oxirane and 4-(1,1,3,3-tetra methylbutyl)phenol) or (Formaldehyde, polymer with oxirane and 4-(1,1,3,3-tetramethylbutyl)phenol) or (p-(1,1,3,3-Tetramethylbutyl)phenol polymer with ethylene oxide and formaldehyde) or (Phenol, 4-(1,1,3,3-tetramethylbutyl)-, polymer with formaldehyde and oxirane)))	PGPB, USPT, USOC, EPAB, JPAB, DWPI	ADJ	YES	ASSIGNEE	07-03-2008
((Bromfenac or Duract or (BROMFENAC SODIUM) or (AHR 10282B) or (Bromfenac monosodium salt sesquihydrate) or (Sodium (2-amino-3-(p-bromobenzoyl)phenyl)acetate sesquihydrate) or (Benzeneacetic acid, 2-amino-3-(4-bromobenzoyl)-, monosodium salt, hydrate (2:3)) or (Benzeneacetic acid, 2-amino-3-(4-bromobenzoyl)-, monosodium salt, sesquihydrate) or (120638-55-3) or (sodium 2-(2-amino-3-(4-bromobenzoyl)phenyl)acetate)) and (Macrocyclon or Tyloxapol or Superinone or Alevaire or Tyloxypal or Superiuone or Enuclene or Exosurf or (Triton A-20) or (Triton WR 1339) or (Triton WR-1339) or "Triton W.R.1339" or Tiloxapol or Tyloxapolum or AIDS094886 or (AIDS-094886) or (NSC 90255) or (p-Isooctylpolyoxyethylenephenol formaldehyde polymer) or (Oxyethylated tertiary octyl-phenol-formaldehyde polymer) or (25301-02-4)	PGPB, USPT, USOC, EPAB, JPAB, DWPI	ADJ	YES	ASSIGNEE	07-03-2008

or (Phenol, p-(1,1,3,3-tetramethylbutyl)-, polymer with ethylene oxide and formaldehyde) or (4-(1,1,3,3-Tetramethylbutyl)phenol, polymer with formaldehyde & oxirane) or (Formaldehyde, polymer with oxirane and 4-(1,1,3,3-tetra methylbutyl)phenol) or (Formaldehyde, polymer with oxirane and 4-(1,1,3,3-tetramethylbutyl)phenol) or (p-(1,1,3,3-Tetramethylbutyl)phenol polymer with ethylene oxide and formaldehyde) or (Phenol, 4-(1,1,3,3-tetramethylbutyl)-, polymer with formaldehyde and oxirane)) and (@pd<20030121 or @ad<20030121 or @rlad<20030121)) and (tyloxapol with bromfenac)					
tyloxapol with bromfenac	PGPB, USPT, USOC, EPAB, JPAB, DWPI	ADJ	YES	ASSIGNEE	07-03-2008
(tyloxapol with bromfenac) and (@pd<20030121 or @ad<20030121 or @rlad<20030121)	PGPB, USPT, USOC, EPAB, JPAB, DWPI	ADJ	YES	ASSIGNEE	07-03-2008
((Bromfenac or Duract or (BROMFENAC SODIUM) or (AHR 10282B) or (Bromfenac monosodium salt sesquihydrate) or (Sodium (2-amino-3-(p-bromobenzoyl)phenyl)acetate sesquihydrate) or (Benzeneacetic acid, 2-amino-3-(4-bromobenzoyl)-, monosodium salt, hydrate (2:3)) or (Benzeneacetic acid, 2-amino-3-(4-bromobenzoyl)-, monosodium salt, sesquihydrate) or (120638-55-3) or (sodium 2-(2-amino-3-(4-bromobenzoyl)phenyl)acetate))) .ti,ab,clm.	PGPB, USPT, USOC, EPAB, JPAB, DWPI	ADJ	YES	ASSIGNEE	07-03-2008
((Macrocyclon or Tyloxapol or Superinone or Alevaire or Tyloxypal or Superiuone or Enuclene or Exosurf or (Triton A-20) or (Triton WR 1339) or (Triton WR-1339) or "Triton W.R.1339" or Tiloxapol or Tyloxapolum or AIDS094886 or (AIDS-094886) or (NSC 90255) or (p-Isooctylpolyoxyethylenephenol formaldehyde polymer) or (Oxyethylated tertiary octyl-phenol-formaldehyde polymer) or (25301-02-4) or (Phenol, p-(1,1,3,3-tetramethylbutyl)-, polymer with ethylene oxide and formaldehyde) or (4-(1,1,3,3-Tetramethylbutyl)phenol, polymer with formaldehyde & oxirane) or (Formaldehyde, polymer	PGPB, USPT, USOC, EPAB, JPAB, DWPI	ADJ	YES	ASSIGNEE	07-03-2008

with oxirane and 4-(1,1,3,3-tetra methylbutyl)phenol) or (Formaldehyde, polymer with oxirane and 4-(1,1,3,3-tetramethylbutyl)phenol) or (p-(1,1,3,3-Tetramethylbutyl)phenol polymer with ethylene oxide and formaldehyde) or (Phenol, 4-(1,1,3,3-tetramethylbutyl)-, polymer with formaldehyde and oxirane))) .ti,ab,clm.					
(tyloxapol or (Triton A-20) or (Triton WR 1339)).ti,ab,clm.	PGPB, USPT, USOC, EPAB, JPAB, DWPI	ADJ	YES	ASSIGNEE	07-03-2008
((Bromfenac or Duract or (BROMFENAC SODIUM) or (AHR 10282B) or (Bromfenac monosodium salt sesquihydrate) or (Sodium (2-amino-3-(p-bromobenzoyl)phenyl)acetate sesquihydrate) or (Benzeneacetic acid, 2-amino-3-(4-bromobenzoyl)-, monosodium salt, hydrate (2:3)) or (Benzeneacetic acid, 2-amino-3-(4-bromobenzoyl)-, monosodium salt, sesquihydrate) or (120638-55-3) or (sodium 2-(2-amino-3-(4-bromobenzoyl)phenyl)acetate)) and (Macrocyclon or Tyloxapol or Superinone or Alevaire or Tyloxypal or Superiuone or Enuclene or Exosurf or (Triton A-20) or (Triton WR 1339) or (Triton WR-1339) or "Triton W.R.1339" or Tiloxapol or Tyloxapolum or AIDS094886 or (AIDS-094886) or (NSC 90255) or (p-Isooctylpolyoxyethylenephenol formaldehyde polymer) or (Oxyethylated tertiary octyl-phenol-formaldehyde polymer) or (25301-02-4) or (Phenol, p-(1,1,3,3-tetramethylbutyl)-, polymer with ethylene oxide and formaldehyde) or (4-(1,1,3,3-Tetramethylbutyl)phenol, polymer with formaldehyde & oxirane) or (Formaldehyde, polymer with oxirane and 4-(1,1,3,3-tetra methylbutyl)phenol) or (Formaldehyde, polymer with oxirane and 4-(1,1,3,3-tetramethylbutyl)phenol) or (p-(1,1,3,3-Tetramethylbutyl)phenol polymer with ethylene oxide and formaldehyde) or (Phenol, 4-(1,1,3,3-tetramethylbutyl)-, polymer with formaldehyde and oxirane)) and (@pd<20030121 or @ad<20030121 or @rlad<20030121)) and (((Bromfenac or Duract or (BROMFENAC SODIUM) or (AHR 10282B) or (Bromfenac monosodium salt sesquihydrate) or (Sodium (2-amino-3-(p-bromobenzoyl)phenyl)acetate sesquihydrate) or (Benzeneacetic acid, 2-amino-3-(4-bromobenzoyl)-, monosodium salt,	PGPB, USPT, USOC, EPAB, JPAB, DWPI	ADJ	YES	ASSIGNEE	07-03-2008

hydrate (2:3)) or (Benzeneacetic acid, 2-amino-3-(4-bromobenzoyl)-, monosodium salt, sesquihydrate) or (120638-55-3) or (sodium 2-(2-amino-3-(4-bromobenzoyl)phenyl)acetate)) .ti,ab,clm.) or ((tyloxapol or (Triton A-20) or (Triton WR 1339)).ti,ab,clm.))					

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of	:	**Confirmation No. 1756**
Shirou SAWA et al.	:	Attorney Docket No. 2005_0232A
Serial No. 10/525,006	:	Group Art Unit 1614
Filed March 28, 2005	:	Examiner Timothy P. Thomas

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

Mail Stop: Amendment

THE COMMISSIONER IS AUTHORIZED TO CHARGE ANY DEFICIENCY IN THE FEES FOR THIS PAPER TO DEPOSIT ACCOUNT NO 23-0975

ADDITIONAL CLAIMS FEE TRANSMITTAL LETTER

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

Sir:

Transmitted herewith is an Amendment in the above-identified application. Additional fees required as a result of this Amendment are calculated as follows:

	SMALL ENTITY		**LARGE ENTITY**
Total Claims exceeding 20 (not already paid for): **16 x**	($ 25 = $)	**or**	($50 = $800.00)
Indep. Claims exceeding 3 (not already paid for): **2 x**	($105 = $)	**or**	($210 = $420.00)
[] Multiple Dep. Claim(s) (if there previously were none): +	($185 = $)	**or**	($370 = $)
Total Additional Fee =	$	**or**	$1,220.00

[] Small entity status of this application has been previously asserted.

[] Small entity status of this application is established by the verified statement under 37 C.F.R. 1.9 and 1.27 which
- [] is enclosed or
- [] has been previously submitted.

[X] A check in the amount of $1,220.00 is enclosed.

[] Please charge Deposit Account No. 23-0975 the amount of $ to cover additional fee. The Commissioner is authorized to charge any deficiency associated with this communication or to credit any overpayment to the Deposit Account. The original and two copies of this document are enclosed.

Respectfully submitted,

Shirou SAWA et al.

By _____
Warren M. Cheek
Registration No. 33,367
Attorney for Applicants

WMC/dlk
Washington, D.C. 20006-1021
Telephone (202) 721-8200
Facsimile (202) 721-8250
March 26, 2008

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of	:	**Confirmation No. 1756**
Shirou SAWA et al.	:	Attorney Docket No. 2005_0232A
Serial No. 10/525,006	:	Group Art Unit 1614
Filed March 28, 2005	:	Examiner Timothy P. Thomas
AQUEOUS LIQUID PREPARATION CONTAINING 2-AMINO-3-(4-BROMOBENZOYL)PHENYLACETIC ACID	:	**Mail Stop: Amendment**

THE COMMISSIONER IS AUTHORIZED TO CHARGE ANY DEFICIENCY IN THE FEES FOR THIS PAPER TO DEPOSIT ACCOUNT NO 23-0975

AMENDMENT

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

Sir:

Responsive to the Official Action dated September 27, 2007, the time for responding thereto being extended for three months in accordance with a petition for extension submitted concurrently herewith, please amend the above-identified application as follows:

Amendments to the Claims

1-18. (Cancelled)

19. (Currently amended) An aqueous liquid preparation comprising at least the following two components, the first component comprising 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof, and the second component comprising an alkyl aryl polyether alcohol type polymer or a polyethylene glycol fatty acid ester.

20. (Previously presented) The aqueous liquid preparation according to claim 19, wherein the alkyl aryl polyether alcohol type polymer is tyloxapol;

wherein the concentration of the tyloxapol is selected from a range of about 0.01 w/v % to about 0.5 w/v %; and

wherein the concentration of the 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof is selected from a range of about 0.01 to about 0.5 w/v %.

21. (Previously presented) The aqueous liquid preparation according to claim 20, wherein the pharmacologically acceptable salt of 2-amino-3-(4-bromobenzoyl)phenylacetic acid is a sodium salt.

22. (Previously presented) The aqueous liquid preparation according to claim 21, wherein the concentration of the 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt is selected from a range of about 0.05 to about 0.2 w/v %.

23. (Previously presented) The aqueous liquid preparation according to claim 22, wherein the concentration of the tyloxapol is selected from a range of about 0.01 w/v % to about 0.3 w/v %.

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

25. (Previously presented) The aqueous liquid preparation according to claim 24, wherein the concentration of the tyloxapol is about 0.02 w/v %.

26. (Previously presented) The aqueous liquid preparation according to claim 25, wherein the formulation further includes one or more additives selected from the group consisting of a preservative, buffer, thickener, stabilizer, chelating agent, and pH controlling agent.

27. (Previously presented) The aqueous liquid preparation according to claim 26, wherein said preservative is benzalkonium chloride; wherein said buffer is boric acid and/or sodium borate; wherein said thickener is polyvinylpyrrolidone; wherein said stabilizer is sodium sulfite; wherein said chelating agent is sodium edetate; and wherein said pH controlling agent is sodium hydroxide.

28. (Previously presented) The aqueous liquid preparation according to claim 27, wherein the pH is from about 7 to about 9.

29. (Previously presented) The aqueous liquid preparation according to claim 28, wherein the pH is from about 7.5 to about 8.5.

30. (Previously presented) The aqueous liquid preparation according to claim 27, wherein said liquid preparation is in the form of an eye drop.

31. (Previously presented) The aqueous liquid preparation according to claim 23, wherein the concentration of the 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt is about 0.2 w/v %.

32. (Previously presented) The aqueous liquid preparation according to claim 31, wherein the concentration of the tyloxapol is about 0.3 w/v %.

33. (Previously presented) The aqueous liquid preparation according to claim 32, wherein the formulation further includes one or more additives selected from the group consisting of a preservative, buffer, thickener, stabilizer, chelating agent, and pH controlling agent.

34. (Previously presented) The aqueous liquid preparation according to claim 33, wherein said preservative is benzalkonium chloride; wherein said buffer is boric acid and/or sodium borate; wherein said thickener is polyvinylpyrrolidone; wherein said stabilizer is sodium sulfite; wherein said chelating agent is sodium edetate; and wherein said pH controlling agent is sodium hydroxide.

35. (Previously presented) The aqueous liquid preparation according to claim 34, wherein said liquid preparation is in the form of an eye drop.

36. (Previously presented) The aqueous liquid preparation according to claim 31, wherein the concentration of the tyloxapol is about 0.02 w/v %.

37. (Previously presented) The aqueous liquid preparation according to claim 36, wherein the formulation further includes one or more additives selected from the group consisting of a preservative, buffer, thickener, stabilizer, chelating agent, and pH controlling agent.

38. (Previously presented) The aqueous liquid preparation according to claim 37, wherein said preservative is benzalkonium chloride; wherein said buffer is boric acid and/or sodium borate; wherein said thickener is polyvinylpyrrolidone; wherein said chelating agent is sodium edetate; and wherein said pH controlling agent is sodium hydroxide.

39. (Withdrawn-currently amended) 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, to obtain an aqueous liquid preparation comprising at least the following two components, the first component comprising 2-amino-3-(4- bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof, and the second component comprising tyloxapol or polyethylene glycol monostearate.

40. (Withdrawn-currently amended) A method for inhibiting decrease in preservative effect of a preservative in an aqueous liquid preparation of 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable 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, to obtain an aqueous liquid preparation comprising at least the following two components, the first component comprising 2-amino-3-(4- bromobenzoyl)phenylacetic acid or a pharmacologically

acceptable salt thereof or a hydrate thereof, and the second component comprising tyloxapol or polyethylene glycol monostearate, together with a preservative.

41. (New) An aqueous liquid preparation consisting essentially of at least the following two components, the first component comprising 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof, and the second component comprising an alkyl aryl polyether alcohol type polymer or a polyethylene glycol fatty acid ester.

42. (New) The aqueous liquid preparation according to claim 41, wherein the alkyl aryl polyether alcohol type polymer is tyloxapol;

wherein the concentration of the tyloxapol is selected from a range of about 0.01 w/v % to about 0.5 w/v %; and

wherein the concentration of the 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof is selected from a range of about 0.01 to about 0.5 w/v %.

43. (New) The aqueous liquid preparation according to claim 42, wherein the pharmacologically acceptable salt of 2-amino-3-(4-bromobenzoyl)phenylacetic acid is a sodium salt.

44. (New) The aqueous liquid preparation according to claim 43, wherein the concentration of the 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt is selected from a range of about 0.05 to about 0.2 w/v %.

45. (New) The aqueous liquid preparation according to claim 44, wherein the concentration of the tyloxapol is selected from a range of about 0.01 w/v % to about 0.3 w/v %.

46. (New) The aqueous liquid preparation according to claim 45, wherein the concentration of the 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt is about 0.1 w/v %.

47. (New) The aqueous liquid preparation according to claim 46, wherein the concentration of the tyloxapol is about 0.02 w/v %.

48. (New) The aqueous liquid preparation according to claim 47, wherein the formulation further includes one or more additives selected from the group consisting of a preservative, buffer, thickener, stabilizer, chelating agent, and pH controlling agent.

49. (New) The aqueous liquid preparation according to claim 48, wherein said preservative is benzalkonium chloride; wherein said buffer is boric acid and/or sodium borate; wherein said thickener is polyvinylpyrrolidone; wherein said stabilizer is sodium sulfite; wherein said chelating agent is sodium edetate; and wherein said pH controlling agent is sodium hydroxide.

50. (New) The aqueous liquid preparation according to claim 49, wherein the pH is from about 7 to about 9.

51. (New) The aqueous liquid preparation according to claim 50, wherein the pH is from about 7.5 to about 8.5.

52. (New) The aqueous liquid preparation according to claim 49, wherein said liquid preparation is in the form of an eye drop.

53. (New) The aqueous liquid preparation according to claim 45, wherein the

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

54. (New) The aqueous liquid preparation according to claim 53, wherein the concentration of the tyloxapol is about 0.3 w/v %.

55. (New) The aqueous liquid preparation according to claim 54, wherein the formulation further includes one or more additives selected from the group consisting of a preservative, buffer, thickener, stabilizer, chelating agent, and pH controlling agent.

56. (New) The aqueous liquid preparation according to claim 55, wherein said preservative is benzalkonium chloride; wherein said buffer is boric acid and/or sodium borate; wherein said thickener is polyvinylpyrrolidone; wherein said stabilizer is sodium sulfite; wherein said chelating agent is sodium edetate; and wherein said pH controlling agent is sodium hydroxide.

57. (New) The aqueous liquid preparation according to claim 56, wherein said liquid preparation is in the form of an eye drop.

58. (New) The aqueous liquid preparation according to claim 53, wherein the concentration of the tyloxapol is about 0.02 w/v %.

59. (New) The aqueous liquid preparation according to claim 58, wherein the formulation further includes one or more additives selected from the group consisting of a preservative, buffer, thickener, stabilizer, chelating agent, and pH controlling agent.

60. (New) The aqueous liquid preparation according to claim 59, wherein said preservative is benzalkonium chloride; wherein said buffer is boric acid and/or sodium borate;

wherein said thickener is polyvinylpyrrolidone; wherein said chelating agent is sodium edetate; and wherein said pH controlling agent is sodium hydroxide.

61. (New) 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, to obtain an aqueous liquid preparation consisting essentially of at least the following two components, the first component comprising 2-amino-3-(4- bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof, and the second component comprising tyloxapol or polyethylene glycol monostearate.

62. (New) 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, to obtain an aqueous liquid preparation consisting essentially of at least the following two components, the first component comprising 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof, and the second component comprising tyloxapol or polyethylene glycol monostearate, together with a preservative.

63. (New) An aqueous liquid preparation consisting of the following two components, the first component comprising 2-amino-3-(4- bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof, and the second component comprising an alkyl aryl polyether alcohol type polymer or a polyethylene glycol fatty acid ester,

and optionally at least one preservative, isotonic, buffer, thickener, stabilizer, chelating agent, pH controlling agent, or perfume.

REMARKS

Favorable reconsideration is respectfully solicited in view of the following remarks.

Initially, Applicant wishes to express its sincere thanks for the courtesy and cooperation provided to its undersigned representative by Examiner Thomas and Examiner Marschel during the personal interview held on March 13, 2008. The following is a summary of the items discussed during the interview.

Claim 19 has been amended as suggested by the Examiners to clarify that the claimed preparation has at least two components, the first component and the second component as described above.

Claims 39 and 40 have been amended consistent with the amendments to claim 19, to allow for rejoinder of these claims upon an allowance of claims 19-38.

New claims 41-63 have been added for additional patent protection. Claims 41-62 correspond to claims 19-40, respectively, except in reciting that the preparation "consists essentially of" the recited components. New claim 63 correponds to claim 19, except that the claim recites "consisting of" the recited components, together with optional components which are supported on page 12, lines 3-11 of the specification.

Turning to the Official Action, item 7 of the Official Action states that the Oath or Declaration is defective because it was not executed. An executed copy of the Declaration was filed on March 28, 2005. A check of the PTO image file history during the interview revealed that an executed copy of the Declaration has been received.

Accordingly, this defect is believed to be overcome.

Claims 19-24 and 31 are rejected under 35 U.S.C. 102 as anticipated by Gamache et al., WO 01/15677. This ground of rejection is respectfully traversed.

The subject matter of the present invention is directed to the specific combination of 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.

On the other hand, Gamache et al. do not disclose this specific combination. Moreover the cited reference is directed to compositions comprising of 5-HT_{1D} and/or HT_{1B} agonists. The cited reference states that these agonists may be combined with an extensive list of other pharmaceutical agents, i.e. (1) anti-microbial agent, (2) anti-inflammatory agents or (3) anti-allergy agent (please see page 6, lines 1-3 of Gamache).

In addition, Gamache et al. only describes "bromfenac" as one of many examples of anti-inflammatory agents enumerated on page 12, lines 11-24. Gamache et al. does not concretely describe nor suggest the claimed preparation containing bromfenac.

Further, although tyloxapol (0.05% w/v) is added to an 1B/1D agonist (0.1-1.0% w/v) and moxifloxacin (0.3% w/v) in Example 4 (an Example of an otic/nasal suspension), there is no explanation about tyloxapol in the description of Gamache et al. or why it is included. Moreover in this Example, moxifloxacin is incorporated as a well-known antibacterial agent but is not an anti-inflammatory agent like bromfenac. Thus it is unclear from Gamache et al. why tyloxapol is added to the otic/nasal suspension containing 1B/1D agonist and moxifloxacin.

"Tyloxapol" described in Example 4 is just a single word description and does not give any clues and hints to the present invention. Therefore, the word "tyloxapol" described only in Example 4 does not destroy the novelty of the present invention.

Besides, Gamache et al. is silent about an alkyl aryl polyether alcohol type polymer or a polyethylene glycol fatty acid ester component according to the preparation of the present invention.

Thus, Gamache et al. neither describe or suggest the specific claimed preparation of the present invention.

As discussed during the interview, it is respectfully submitted that the disclosure of Gamache et al. does not constitute an "anticipation" of the claimed invention under 35 U.S.C. 102. It is not possible to envision the specific claimed combination from the great number of possible combinations suggested by the cited reference.

As stated by the Board of Appeals in a similar case many years ago,

"While the invention here claimed in its broader aspect is doubtless embraced within the

speculative teachings of the references, we doubt if references which are not directed to the same purpose and do not have the same inventive concept, can be fairly applied in rejecting claims such as those on appeal where anticipation can be found only by making one of a very great number of possible permutations which are covered by the reference disclosures. The likelihood of producing a composition such as here claimed from a disclosure such as shown by the Dykstra patent would be about the same as the likelihood of discovering the combination of a safe from a mere inspection of the dials thereof."

Ex parte Garvey, 41 USPQ 583 (POBA 1939). See also Ex parte Starr, 44 USPQ 545 (POBA 1938); and Application of Luvisi, 52 CCPA 1063 (CCPA 1963).

See also M.P.E.P. 2131.02, discussing In re Meyer, 202 USPQ 175 (CCPA 1979) (A reference disclosing "alkaline chlorine or bromine solution" embraces a large number of species and cannot be said to anticipate claims to "alkali metal hypochlorite.").

For the foregoing reasons, it is respectfully submitted that the claimed invention is novel over Gamache et al.

Applicant gratefully acknowledges the Examiners' indication during the interview that this ground of rejection would be withdrawn.

Claim 19 is rejected under 35 U.S.C. 102 as anticipated by Dobrozsi, U.S. 6,319,513. This ground of rejection is respectfully traversed for the same reasons as stated above regarding the rejection over Gamache et al.

Dobrozsi discloses compositions comprising colloidal particles selected from the group consisting of silica, titanium dioxide, clay, and mixtures thereof. To the colloidal particle compositions may be added a great number of additional ingredients such as (1) analgesics, (2) decongestants, (3) expectorants, (4) antitussives, (5) antihistamines, (6) broncholilator, (7) topical anesthetics, (8) sensory agents, (9) oral care agents, (10) miscellaneous respiratory agents, (11) gastrointestinal agents, and mixtures thereof (please see column 2, lines 33-45 of Dobrozsi).

Dobrozsi describes on column 9, line 66 - column 10, line 11 that "[t]he analgesics useful for this invention include any narcotic and non-narcotic analgesics, such as --- bromfenac, ---". That is, Dobrozsi only describes "bromfenac" as one of so many examples of agents enumerated.

Further, Dobrozsi does not describe nor suggest an alkyl aryl polyether alcohol type polymer or a polyethylene glycol fatty acid ester component according to the preparation of the

present invention.

Besides, Dobrozsi neither describes nor suggests the specific combination of 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 of the claimed invention.

Although tyloxapol is added to oxymethazoline hydrochloride in the preparation of mucoretentive intrasal spray decongestant (Example 10) on column 23, line 46 in Dobrozsi, no explanation about tyloxapol is given.

Besides, oxymethazoline hydrochloride is a well known adrenergic, and is not an anti-inflammatory agent like bromfenac.

For the same reasons as the 102 rejection over Gamache et al., it is respectfully submitted that the present invention is novel over Dobrozsi.

Applicant gratefully acknowledges the Examiners' indication during the interview that this ground of rejection would be withdrawn.

Claims 19-38 are further rejected under 35 U.S.C. 102(e) as being anticipated by Sawa, U.S. 2007/0082857. This ground of rejection is respectfully traversed.

The cited reference is a published U.S. patent application of a U.S. national stage application based upon PCT/JP04/16849 filed November 12, 2004. International Application No. PCT/JP2004/016849 was published in Japanese language under Publication No. WO2005/046700. Please see Appendix A. Accordingly, the published patent application has no 102(e) date, nor does the published international application WO2005/046700 have a 102(e) date. Please see Appendix B, which is a copy of Example 5 of the Examination Guidelines for 35 U.S.C. 102(e) published by the USPTO.

Accordingly, the earliest effective date of the cited reference as a prior art reference is its publication date of April 12, 2007. Moreover, the earliest effective date of the published international application WO2005/046700 is its publication date of May 26, 2005.

In conclusion, the cited reference is not available as prior art against the present invention, and this ground of rejection should be withdrawn.

Applicant gratefully acknowledges the Examiners' indication during the interview that this ground of rejection would be withdrawn.

Claims 19-29, 31-34 and 36-38 are rejected under 35 U.S.C. 103 as being unpatentable over Gamache et al. and ISTA Pharmaceuticals or Nolan et al. (abstract). This ground of rejection is respectfully traversed.

The essential features of the preparation of the present invention cannot be derived from the combination of Gamache et al. and ISTA Pharmaceuticals or Nolan (abstract).

Gamache et al. is discussed above. This reference does not suggest the claimed invention. Gamache et al. is directed to 5-HT agonist compositions with a great number of other possible ingredients. The reference does not suggest the claimed aqueous liquid preparation comprises at least the following two components according to claims 19-38, the first component comprising 2-amino-3-(4- bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof, and the second component comprising an alkyl aryl polyether alcohol type polymer or a polyethylene glycol fatty acid ester.

Regarding claims 41-60, the claim recites the transitional phrase "consisting essentially of" means that the claim is limited to the specified ingredients and those that do not materially affect the basic and novel characteristics of the claimed invention. See M.P.E.P. 2111.03.

It is respectfully submitted that the principal 5-HT agonist of the Gamache composition would affect the basic novel properties of the claimed preparation.

The Examiners indicated during the interview that this amendment would be helpful to overcome this ground of rejection.

The cited ISTA publication was discussed during the interview. Although the cited reference has a publication date of May 25, 2004 after the effective U.S. filing date of the instant application, the reference is cited for its statement that "ISTA acquired U.S. marketing rights for Xibrom in May 2002 under a license from Senju." Thus the rejection is based upon the position that the claimed invention was known by others in the U.S. prior to the effective filing date of the instant application in the U.S. of January 16, 2004. And since the knowledgeable person(s) of ISTA is not an inventor of the invention, the reference is available as a reference under 35 U.S.C.

102(a), i.e. there is no one year grace period under 35 U.S.C. 102(b).

It should be noted that the cited reference does not disclose the claimed preparation. It does disclose a "bromfenac sodium ophthalmic solution", but it does not disclose the second claimed component comprising an alkyl aryl polyether alcohol type polymer or a polyethylene glycol fatty acid ester. Nevertheless, it is understood that the PTO position is that the reference is being cited for the proposition that the claimed preparation was known in the U.S. by ISTA before the effective filing date of the instant application.

Upon inquiry, it has been determined that Xibrom has a different composition from the claimed preparation. Enclosed is a copy of the Product Insert and Material Safety Data Sheet as Appendix C. An examination of these documents show that Xibrom contains no alkyl aryl polyether alcohol type polymer or polyethylene glycol fatty acid ester, which is the second component of the claimed preparation.

There is also enclosed a ISTA Press Release about Xibrom, which states that "Xibrom, under a different trade name but identical formulation, was launched in Japan in 2000 by Senju Pharmaceuticals Co. Ltd. ISTA acquired U.S. marketing rights for Xibrom in 2002 and launched the product in the U.S. in 2005." Please see the attached Appendix D.

In summary, the cited ISTA reference fails to suggest that the claimed preparation was known in the U.S. prior to the effective filing date of the instant application. Moreover the cited ISTA reference in combination with Gamache et al. does not suggest the claimed invention.

Regarding the alternative secondary reference Nolan, only the abstract of Nolan was cited in the rejection and included with the Office Action. The abstract only teaches that bromfenac is a potent anti-inflammatory agent. It does not disclose the claimed second component. Therefore the combination of Nolan (abstract) with Gamache et al. does not suggest the claimed preparation comprising the at least two components.

Applicant acknowledges that a complete copy of Nolan was provided to the Applicant's representative during the interview. The complete copy of the reference will be studied for its relevance and additional comments will be provided if possible.

Nevertheless, it is respectfully submitted that neither Gamache et al., ISTA

Pharmaceuticals and/or Nolan disclose or suggest the claimed preparation as amended, because they do not disclose the claimed preparation comprises the at least first and second claimed components.

Regarding new claims 41-60, even if one skilled in the art would have been motivated to modify the Gamache et al. composition in view of ISTA and Nolan, the artisan would have still obtained a 5-HT agonist composition, which is excluded from the amended claims by the "consisting essentially of" transitional phrase.

For the foregoing reasons, Applicant submits that the present invention is unobvious from Gamache et al. and ISTA Pharmaceuticals or Nolan to those skilled in the art.

Claims 19-30 are rejected under 35 U.S.C. 103 as unpatentable over Yakuji Nippo Ltd. and Xia, U.S. 6,369,112. This ground of rejection is respectfully traversed.

As stated in the rejection, the Yakuji reference teaches a bromfenac solution. It does not teach tyloxapol. Xia teaches adding tyloxapol to a contact lens solution to improve stability of the solution.

However Xia teaches adding tyloxapol to the contact lens solution for the purpose of improving stability of the biguanide disinfection agent in the solution. See the abstract and column 1, lines 10-12.

On the other hand, the claimed invention does not contain a biguanide. Furthermore the preparation of Yakuji contains bromfenac and does not contain any biguanide, according to the partial translation of record. Bromfenac is structurally very different from a biguanide.

Therefore it is respectfully submitted that one skilled in the art would not have been motivated to add tyloxapol taught by Xia to the composition of Yakuji for the purpose of stabilizing bromfenac.

Therefore, it is respectfully submitted that the present invention is unobvious from Yakuji Nippo Ltd. and Xia.

There is concurrently filed herewith an Information Disclosure Statement. As suggested by the Examiners, a complete English Translation of Yakuji is cited in the IDS and enclosed herewith. Also enclosed and cited is a corrected partial English translation of Yakuji.

Claims 19-38 are further rejected under 35 U.S.C. 103 as unpatentable over Yakuji Nippo Ltd. and Xia and Nolan (abstract). This ground of rejection is respectfully traversed.

The teachings of Yakuji and Xia are discussed above. Nolan (abstract) fails to remedy the deficiencies of Yakuji and Xia. There is no teaching or suggestion in the cited references for combining tyloxapol, or any alkyl aryl polyether alcohol type polymer or polyethylene glycol fatty acid ester, with bromfenac, or a 2-amino-3-(4- bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof, to obtain the claimed preparation.

Accordingly, this ground of rejection is respectfully submitted to be overcome.

Applicant gratefully acknowledges the Examiners' indication during the interview that this ground of rejection should be overcome.

Lastly, claims 19-38 are provisionally rejected on the ground of non-statutory obviousness-type double patenting as being unpatentable over claims 1-43 of copending application Serial No. 11/755,662.

The Examiner is respectfully requested to hold this provisional ground of rejection in abeyance until a later date. Upon overcoming all other grounds of rejection, it is respectfully submitted that this provisional ground of rejection should be withdrawn and the application passed on to allowance.

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

Respectfully submitted,

Shirou SAWA et al.

By: Warren M. Cheek

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

WMC/dlk
Washington, D.C. 20006-1021
Telephone (202) 721-8200
Facsimile (202) 721-8250
March 26, 2008

Search result: 1 of 1

(WO/2005/046700) AQUEOUS SOLUTION PREPARATION CONTAINING AMINOGLYCOSIDE ANTIBIOTIC AND BROMFENAC

Biblio. Data | Description | Claims | National Phase | Notices | Documents

Latest bibliographic data on file with the International Bureau

Publication Number: WO/2005/046700 **International Application No.:** PCT/JP2004/016849
Publication Date: 26.05.2005 **International Filing Date:** 12.11.2004

Int. Class.: ***A61K 31/196*** (2006.01), ***A61K 31/7036*** (2006.01), *A61K 9/00* (2006.01)

Applicants: **SENJU PHARMACEUTICAL CO., LTD.** [JP/JP]; 5-8, Hiranomachi 2-chome, Chuo-ku, Osaka-shi, Osaka, 5410046 (JP) *(All Except US)*.
SAWA, Shirou [JP/JP]; 366-1-105, Minamibefu 4-chome, Nishi-ku, Kobe-shi, Hyogo, 6512116 (JP) *(US Only)*.

Inventor: **SAWA, Shirou** [JP/JP]; 366-1-105, Minamibefu 4-chome, Nishi-ku, Kobe-shi, Hyogo, 6512116 (JP).

Agent: **IWATANI, Ryo**; ORIX Dojima Bldg. 3F, 1-31, Dojima 2-chome, Kita-ku, Osaka-shi, Osaka 530-0003 (JP).

Priority Data: 2003-384646 14.11.2003 JP

Title: AQUEOUS SOLUTION PREPARATION CONTAINING AMINOGLYCOSIDE ANTIBIOTIC AND BROMFENAC

Abstract: Stable and clear aqueous solution preparations comprising aminoglycoside antibiotics or a pharmacologically acceptable salt thereof and bromfenac being a nonsteroid antiinflammatory agent or a pharmacologically acceptable salt thereof.

Designated States: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.
African Regional Intellectual Property Org. (ARIPO) (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW)
Eurasian Patent Organization (EAPO) (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM)
European Patent Office (EPO) (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR)
African Intellectual Property Organization (OAPI) (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Publication Language: Japanese (JA)

Filing Language: Japanese (JA)

APPENDIX A

Examination Guidelines for 35 U.S.C. § 102(e), as amended by the American Inventors Protection Act of 1999, and further amended by the Intellectual Property and High Technology Technical Amendments Act of 2002, and 35 U.S.C. § 102(g)

This notice sets forth the interpretation by the United States Patent and Trademark Office (USPTO or Office) of 35 U.S.C. §§ 102(e) and 374, as amended by the American Inventors Protection Act of 1999 (AIPA) (Pub. L. 106-113, 113 Stat. 1501 (1999)), and as further amended by the Intellectual Property and High Technology Technical Amendments Act of 2002 (H.R. 2215) (Pub. L. 107-273, 116 Stat. 1758 (2002)). This notice also clarifies the Office's policy on prior art rejections based on 35 U.S.C. § 102(g).

Generally, 35 U.S.C. § 102(e), after enactment of the AIPA and H.R. 2215, is similar to the pre-AIPA § 102(e), with two significant differences, which may be summarized as: (1) in addition to U.S. patents, now certain **publications** of U.S. and international applications may be applied as of their filing dates in a prior art rejection; and (2) **certain international filing dates** are now U.S. filing dates for prior art purposes under § 102(e), and U.S. patents and certain application publications may now be applied as of these international filing dates in a prior art rejection.

Specifically, this notice provides guidance that prior art, as defined by § 102(e) of the patent code in effect on November 29, 2000, includes U.S. patents, publications of U.S. patent applications and World Intellectual Property Organization's (WIPO) publications of international applications, provided such references do not directly or indirectly result from an international application filed before November 29, 2000. If a U.S. patent resulted from an international application filed before November 29, 2000, the U.S. patent will have a prior art date per § 102(e) in effect prior to November 29, 2000, which is the earlier of the date of compliance with § 371(c)(1), (2) and (4) of the patent code (e.g. National Stage entry) or the filing date of the later-filed U.S. application that claimed the benefit of the international application. A U.S. or WIPO publication of an international application filed prior to November 29, 2000 will have no prior art effect under § 102(e). Such publications do, however, have prior art effect under § 102(a) or (b) as of their publication dates.

Furthermore, all pending U.S. patent applications being examined, and all U.S. patents being reexamined, or otherwise being contested, whenever filed, are subject to the amended version of § 102(e).

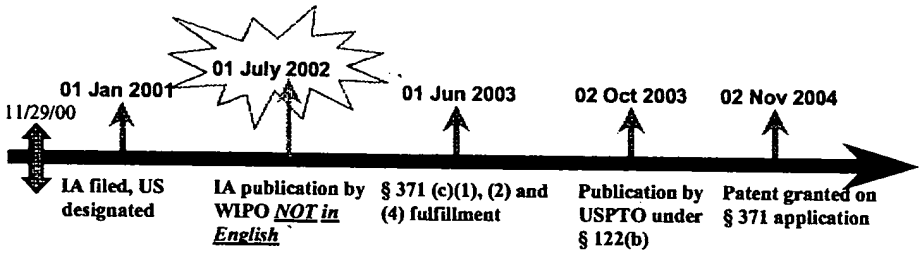
This notice also provides examples of the determination of § 102(e) dates for references based on the most common factual scenarios. The examples that best highlight the recent change to §§ 102(e) and 374 are the examples that involve a WIPO publication of an international application under PCT Article 21(2), a U.S. publication of an international application, or a U.S. patent derived from an international application.

The policy and practice set forth in the Official Gazette Notice entitled "Examination Guidelines for 35 U.S.C. § 102(e)(2), as amended by the American Inventors Protection

APPENDIX B

Example 5: References based on the **National Stage (§ 371)** of an **International Application filed on or after November 29, 2000** and which was **not** published in **English** under PCT Article 21(2).

All references, whether the WIPO publication, the U.S. application publication or the U.S. patent, of an international application (IA) that were filed on or after November 29, 2000 but were **not** published in **English** under PCT Article 21(2) have no § 102(e) prior art date at all. According to § 102(e), no benefit of the international filing date (nor any U.S. filing dates prior to the IA) is given for § 102(e) prior art purposes if the IA was published under PCT Article 21(2) in a language other than English. Such references may be applied under § 102(a) or (b) as of their publication dates, but never under § 102(e).



The § 102(e)(1) date for the IA publication by WIPO is: None
The § 102(e)(1) date for Publication by USPTO is: None
The § 102(e)(2) date for the Patent is: None

The IA publication by WIPO can be applied under § 102(a) or (b) as of its publication date (01 July 2002).

Additional Priority/Benefit Claims:

- ✓ If the IA properly claimed priority/benefit to any earlier-filed U.S. application (whether provisional or nonprovisional), there would still be no § 102(e) date for all the references.
- ✓ If a later-filed U.S. nonprovisional (§ 111(a)) application claimed the benefit of the IA in the example above, the § 102(e) date of the patent or publication of the later-filed U.S. application would be the actual filing date of the later-filed U.S. application.

Example 6: References based on the **National Stage (§ 371)** of an **International Application filed prior to November 29, 2000** (language of the publication under PCT Article 21(2) is not relevant)

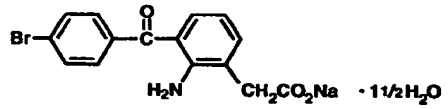
The reference U.S. patent issued from an international application (IA) that was filed prior to November 29, 2000 has a § 102(e) prior art date of the date of fulfillment of the requirements of 35 U.S.C. § 371(c)(1), (2) and (4). This is the pre-AIPA § 102(e). The

Xibrom™
(bromfenac ophthalmic solution) 0.09%

STERILE

DESCRIPTION

XIBROM (bromfenac ophthalmic solution) 0.09% is a sterile, topical, nonsteroidal anti-inflammatory drug (NSAID) for ophthalmic use. Each mL of Xibrom contains 1.035 mg bromfenac sodium (equivalent to 0.9 mg bromfenac free acid). Bromfenac sodium is designated chemically as sodium 2-amino-3-(4-bromobenzoyl) phenylacetate sesquihydrate, with an empirical formula of $C_{15}H_{11}BrNNaO_3 \cdot 1\ 1/2\ H_2O$. The structural formula of bromfenac sodium is:



Bromfenac sodium is a yellow to orange crystalline powder. The molecular weight of bromfenac sodium is 383.17. XIBROM ophthalmic solution is supplied as a sterile aqueous 0.09% solution, with a pH of 8.3. The osmolality of XIBROM ophthalmic solution is approximately 300 mOsmol/kg. Each mL of XIBROM ophthalmic solution contains: **Active:** bromfenac sodium hydrate 0.1035%. **Inactives:** benzalkonium chloride (0.05 mg/mL), boric acid, disodium edetate (0.2 mg/mL), polysorbate 80 (1.5 mg/mL), povidone (20 mg/mL), sodium borate, sodium sulfite anhydrous (2 mg/mL), sodium hydroxide to adjust the pH, and purified water, USP.

Clinical Pharmacology:

Mechanism of Action:

Bromfenac is a nonsteroidal anti-inflammatory drug (NSAID) that has anti-inflammatory activity. The mechanism of its action is thought to be due to its ability to block prostaglandin synthesis by inhibiting cyclooxygenase 1 and 2. Prostaglandins have been shown in many animal models to be mediators of certain kinds of intraocular inflammation. In studies performed in animal eyes, prostaglandins have been shown to produce disruption of the blood-aqueous humor barrier, vasodilation, increased vascular permeability, leukocytosis, and increased intraocular pressure.

Pharmacokinetics:

The plasma concentration of bromfenac following ocular administration of 0.09% XIBROM (bromfenac ophthalmic solution) in humans is unknown. Based on the maximum proposed dose of one drop to each eye (0.09mg) and PK information from other routes of administration, the systemic concentration of bromfenac is estimated to be below the limit of quantification (50 ng/mL) at steady-state in humans.

Clinical Trials:

Clinical efficacy was evaluated in two randomized, double-masked, vehicle-controlled U.S. trials in which subjects with a summed ocular inflammation score ≥3 after cataract surgery were assigned to XIBROM or vehicle in a 2:1 ratio following surgery. One drop of XIBROM or vehicle was self-instilled in the study eye twice a day for 14 days, beginning the day after surgery. The primary endpoint was reduction of ocular inflammation (to trace inflammation or clearing) assessed 14 days post-surgery using a slit lamp binocular microscope. In the intent-to-treat analyses of both studies, a significant effect of XIBROM on ocular inflammation after cataract surgery was demonstrated (62-66% vs. 40-48%). An additional efficacy end point was the time required for resolution of ocular pain in subjects who reported pain. Overall, only 20% of the patients undergoing cataract surgery in these trials had pain on the first day after surgery. In these patients, the XIBROM group demonstrated a statistically significant difference in median time to resolution of ocular pain of 2 days compared to 4 days for patients receiving vehicle.

Indications and Usage:

XIBROM ophthalmic solution is indicated for the treatment of postoperative inflammation and the reduction of ocular pain in patients who have undergone cataract extraction.

Contraindications:

XIBROM ophthalmic solution is contraindicated in patients with known hypersensitivity to any ingredient in the formulation.

Warnings:

Contains sodium sulfite, a sulfite that may cause allergic-type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in nonasthmatic people.

There is the potential for cross sensitivity to acetylsalicylic acid, phenylacetic acid derivatives, and other NSAIDs. Therefore, caution should be used when treating individuals who have previously exhibited sensitivities to these drugs.

With some NSAIDs, there exists the potential for increased bleeding time due to interference with platelet aggregation. There have been reports that ocularly applied NSAIDs may cause increased bleeding of ocular tissues (including hyphemas) in conjunction with ocular surgery.

Precautions:

General:

All topical nonsteroidal anti-inflammatory drugs (NSAIDs) may slow or delay healing. Topical corticosteroids are also known to slow or delay healing. Concomitant use of topical NSAIDs and topical steroids may increase the potential for healing problems.

Use of topical NSAIDs may result in keratitis. In some susceptible patients, continued use of topical NSAIDs may result in epithelial breakdown, corneal thinning, corneal erosion, corneal ulceration or corneal perforation. These events may be sight threatening. Patients with evidence of corneal epithelial breakdown should immediately discontinue use of topical NSAIDs and should be closely monitored for corneal health.

Postmarketing experience with topical NSAIDs suggests that patients with complicated ocular surgeries, corneal denervation, corneal epithelial defects, diabetes mellitus, ocular surface diseases (e.g., dry eye syndrome), rheumatoid arthritis, or repeat ocular surgeries within a short period of time may be at increased risk for corneal adverse events which may become sight threatening. Topical NSAIDs should be used with caution in these patients.

Postmarketing experience with topical NSAIDs also suggests that use more than 24 hours prior to surgery or use beyond 14 days post surgery may increase patient risk for the occurrence and severity of corneal adverse events.

It is recommended that XIBROM ophthalmic solution be used with caution in patients with known bleeding tendencies or who are receiving other medications which may prolong bleeding time.

Information for Patients:

XIBROM ophthalmic solution should not be administered while wearing contact lenses.

Carcinogenesis, Mutagenesis, Impairment of Fertility:

Long term carcinogenicity studies in rats and mice given oral doses of bromfenac up to 0.6 mg/kg/day (360 times the recommended human ophthalmic dose [RHOD] of 1.67 µg/kg in 60 kg person on a mg/kg/basis, assuming 100% absorbed) and 5.0 mg/kg/day (3000 times RHOD), respectively revealed no significant increases in tumor incidence.

Bromfenac did not show mutagenic potential in various mutagenicity studies, including the reverse mutation, chromosomal aberration, and micronucleus tests.

Bromfenac did not impair fertility when administered orally to male and female rats at doses up to 0.9 mg/kg/day and 0.3 mg/kg/day, respectively (540 and 180 times RHOD, respectively).

Pregnancy: Teratogenic Effects: Pregnancy Category C.

Reproduction studies performed in rats at oral doses up to 0.9 mg/kg/day (540 times RHOD) and in rabbits at oral doses up to 7.5 mg/kg/day (4500 times RHOD) revealed no evidence of teratogenicity due to bromfenac. However, 0.9mg/kg/day in rats caused embryo-fetal lethality, increased neonatal mortality, and reduced postnatal growth. Pregnant rabbits treated with 7.5 mg/kg/day caused increased post-implantation loss.

There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Non-Teratogenic Effects:

Because of the known effects of prostaglandin biosynthesis-inhibiting drugs on the fetal cardiovascular system (closure of ductus arteriosus), the use of XIBROM ophthalmic solution during late pregnancy should be avoided.

Nursing Mothers:

Caution should be exercised when XIBROM ophthalmic solution is administered to a nursing woman.

Pediatric Use:

Safety and efficacy in pediatric patients below the age of 18 have not been established.

Geriatric Use:

There is no evidence that the efficacy or safety profiles for XIBROM differ in patients 65 years of age and older compared to younger adult patients.

Adverse Reactions:

The most commonly reported adverse experiences reported following use of XIBROM after cataract surgery include: abnormal sensation in eye, conjunctival hyperemia, eye irritation (including burning/stinging), eye pain, eye pruritus, eye redness, headache, and iritis. These events were reported in 2-7% of patients.

Clinical Practice: The following events have been identified during postmarketing use of bromfenac ophthalmic solution 0.09% in clinical practice. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. The events, which have been chosen for inclusion due to either their seriousness, frequency of reporting, possible causal connection to topical bromfenac ophthalmic solution 0.09%, or a combination of these factors, include corneal erosion, corneal perforation, corneal thinning, and epithelial breakdown **(see PRECAUTIONS, General)**.

Dosage and Administration:

For the treatment of postoperative inflammation and the reduction of ocular pain in patients who have undergone cataract extraction, one drop of XIBROM ophthalmic solution should be applied to the affected eye(s) two times daily beginning 24 hours after cataract surgery and continuing through the first 2 weeks of the postoperative period.

How Supplied:

XIBROM™ (bromfenac ophthalmic solution) 0.09% is supplied in a white LDPE plastic squeeze bottle with a 15 mm LDPE white dropper-tip and 15 mm polypropylene gray cap as follows:

NDC 67425-004-50 5 mL in 10 mL container
NDC 67425-004-12 2.5 mL in 7.5 mL container

Storage

Store at 15-25°C (59-77°F)

Rx Only

U.S. Patent No: 4,910,225

Manufactured for: ISTA Pharmaceuticals®, Inc., Irvine, CA 92618
By: Bausch & Lomb Incorporated, Tampa, FL 33637
Under license from: Senju Pharmaceuticals Co., Ltd., Osaka, Japan 541-0046
Issued Date: March 2006
Printed in USA

XIB509-7/06

APPENDIX C

ISTA Pharmaceuticals, Inc.
MATERIAL SAFETY DATA SHEET
Xibrom (bromfenac ophthalmic solution) 0.09%

PRODUCT AND COMPANY INFORMATION

Product Name:	Xibrom (bromfenac ophthalmic solution) 0.09%
Generic Name:	Bromfenac ophthalmic solution 0.09% (0.1% solution of Sodium 2-amino-3-(4-bromobenzoyl) phenylacetate sesquihydrate)
NDC No.	67425-004-50 (5mL) and 67425-004-25 (2.5mL)
Legal Category:	Investigational drug, filled in bottle with controlled tip and overpacked inside a cardboard carton.
Drug Composition:	Contains a non steroidal anti-Inflammatory

Company Name: ISTA Pharmaceuticals, Inc.
Company Address: 15295 Alton Parkway, Irvine, CA 92618
Telephone Number: 949-788-6000 (Monday-Friday: 8:00am – 5:00pm PST)

Emergency Phone Number: 24 hours; Infotrack 1-800-535-5053

Preparation Date: May 03, 2005 (Version 05.03.05 – 01)

2. COMPOSITION/INFORMATION ON INGREDIENTS

Description	CAS#	TLV (mg/m^3)	PEL (mg/m^3)	% Content
Bromfenac Sodium Sesquihydrate	91714-93-1	NE	NE	0.1%
Sodium Borate	1303-96-4	NE	NE	>1%
Polyvinylpyrrolidone	252498-54-1	NE	NE	>1%
Purified Water	7732-18-5	NE	NE	>1%

Ingredients <1% - Boric Acid, Sodium Sulfite, Disodium Edetate, Polysorbate 80, Benzalkonium Chloride

3. HAZARDS identification

****

EMERGENCY OVERVIEW

Presents little or no hazards if spilled and no unusual hazard if involved in fire.

****

POTENTIAL HEALTH HAZARDS

Carcinogenicity: **(NTP)** No **(IARC)** No **(OSHA)** No

Eye: Irritant with some individuals

Skin: Irritant

Ingestion: Gastric exposure of large doses has been associated with ulceration and necrosis of gastrointestinal structures, as well as severe liver damage. Injestion of large doses may cause central nervous system effects, including drowsiness, dizziness, and vision disorders. Effects of injestion of lower doses, as present in the ophthalmic solution are unknown. Avoid unnecessary exposure.

Inhalation: Irritant.

Chronic Effects: Chronic ingestion of larger doses can cause severe liver damage. Chronic oral exposure of large doses may be associated with gastrointestinal disturbances, such as nausea, vomiting, heartburn and epigastric pain. Central nervous system effects may include drowsiness, dizziness, and vision disorders.

Target Organs: Liver, gastrointestinal system and central nervous system.

Medical Conditions Aggravated by Long Term Exposure: Avoid unnecessary exposure. Pre-existing liver or gastrointestinal conditions may be aggravated.

4. FIRST AID MEASURES

Eyes: Rinse immediately with copious amounts of water for at least 20 minutes. Contact a physician.

Skin: Remove all contaminated clothing and wash skin with copious amounts of water for at least 20 minutes. Contact physician if skin becomes irritated.

Ingestion: Wash out mouth and drink plenty of water and bland fluids. The use of an emetic drug and/or gastric lavage is advisable. Do not give anything to an unconscious person. Contact physician.

Inhalation: Remove person to fresh air, and if breathing stops, use artificial respiration. Contact physician.

Note to Physicians: The safety of this product in children has not been established.
Pregnancy: The safety of this product in pregnant women has not been established. This product should be used by pregnant women, or women who may be pregnant, only if expected therapeutic benefits outweigh the possible risks associated with treatment.

Nursing Mothers: The safety of this product in nursing mothers has not been established. This product should be used by nursing mothers, only if expected therapeutic benefits outweigh the possible risks associated with treatment.

Additional details are available on the package insert or in the Physicians Desk Reference.

5. FIRE FIGHTING MEASURES

Flammable Properties: Flash point: NE Method: NE

Hazardous Products: Products of combustion are toxic.

Extinguishing Media: Dry chemical, carbon dioxide, halon, water spray or fog, and foam on surrounding materials.

Fire Fighting Instructions: Wear self-contained breathing apparatus and protective clothing. Use water spray to keep fire-exposed containers cool. Do not spray water into the burning material.

6. ACCIDENTAL RELEASE

Large/Small Spills: Use personal protective equipment. Absorb spill with inert material (e.g. vermiculite, sand or earth), then place in suitable container. Contain the spill to prevent drainage into sewers, drains or streams. Dispose of material according to Federal, State and Local regulations.

7. HANDLING AND STORAGE

Handling: Avoid contact with product and use caution to prevent puncturing containers. No special protective equipment or procedures are required in the clinical or home environment.

Storage: Store product upright in original containers with the cap tightly closed at a controlled room temperature 15^0-30^0 C (59^0- 86^0 F). **KEEP THIS AND ALL DRUGS OUT OF THE REACH OF CHILDREN.**

8. EXPOSURE CONTROL/PERSONAL PROTECTION

Engineering Controls: When manufacturing this product in the manufacturing plant, provide adequate ventilation for the raw material handling and compounding process, which will maintain the dust and vapor levels below the TLV, STEL, and PEL values for the ingredients. Ventilation fans should be explosion proof. Use adequate personal protective equipment e.g. NIOSH-approved respirators, goggles or safety glasses, gloves and protective clothing. Ensure training in the handling of chemical material and use current Material Safety Data Sheets.

Eye Protection: (29 CFR 1910.133) Recommend goggles or chemical safety glasses when working with this product in the industrial setting.

Skin Protection: Thick impermeable gloves and protective clothing when manufacturing this product in the industrial setting.

Respiratory Protection: (29 CFR 1910.134) NIOSH approved respirator, with organic vapor, acid gas and HEPA filter recommended for handling raw materials. **Warning: Do not use air-purifying respirators in oxygen-depleted environments**. No respiratory protection is required in the clinical or home environment.

Other: None

Ventilation: Recommended in the industrial setting.

Contaminated Equipment: Wash contaminated clothing separately. Wash contaminated equipment with soap and water. Release rinse water into an approved wastewater system or according to Federal, State and Local regulations.

9. CHEMICAL & PHYSICAL PROPERTIES

Appearance & Odor: Clear Yellow Colored Solution

Boiling Point:	NE	Evaporation Rate:	NE
Specific Gravity:	1.0	Vapor Density:	NE
Vapor Pressure:	NE	Viscosity:	NE
Water Solubility:	Miscible	Percent Volatile by Volume:	<1

10. STABILITY AND REACTIVITY

Chemical Stability: Stable

Conditions to avoid: Extreme heat or cold.

Incompatibility: This product has the incompatibilities of water e.g. strong acids, bases, alkali metals, alkali hydrides and silver preparations.

Hazardous Decomposition Products: Products of combustion are toxic.

Hazardous Polymerization: Should not occur and has not been reported.

11. TOXICOLOGY

Summary of Risks: The toxicological information in this MSDS refers to the effects of the active ingredient (bromfenac sodium). Concentrations and toxicological effects are substantially reduced in the ophthalmic solution. For more detailed information see MSDS on bromfenac sodium (code 002990). Severe liver damage has been reported in patients who have taken multiple doses of an oral dosage form containing significantly higher concentrations of bromfenac sodium than are present in the ophthalmic solution.

CAS # 91714-93-1 **Bromfenac Sodium**
Bromfenac Sodium is known to cause liver damage in humans and or death when administered orally at therapeutic doses (at a concentration significantly higher than for the ophthalmic solution) for greater than ten days.

12. ECOLOGICAL INFORMATION

Chemical Fate Information: Product administered to patients presents a negligible impact on the environment.

13. DISPOSAL INFORMATION

Dispose of material according to Federal, State, and Local regulations. The method typically used is incineration.

EPA Designations: RCRA Hazardous Waste: Not Listed

SARA Title III: Not Listed

14. TRANSPORTATION INFORMATION

Transportation Data: Not classified as hazardous by DOT regulations.

15. REGULATORY INFORMATION

DOT Designations: Not classified as hazardous by DOT regulations.

EPA Designations: RCRA Hazardous Waste
(40 CFR 261.33) Not Listed

FDA Designations: Prescription only medication.
NDC No.: 67425-004-050 (5mL
and 67425-004-25 (2.5mL)

OSHA Designations: (29 CFR 1910.1000, Table Z)
Not Listed

SARA Title III: Not listed under Section 313 of Toxic Release Reporting.

CALIFORNIA PROPOSITION 65: Not Listed

16. OTHER INFORMATION

None

The information contained herein is furnished without warranty of any kind. The above information is believed to be correct but does not purport to be all-inclusive and should be used only as a guide. Users should make independent determinations of the suitability and completeness of information from all sources to assure proper use and disposal of these materials and the safety and health of employees and customers. In no way shall the company be liable for any claims, losses, or damages of any third party or for lost profits of any special, indirect, incidental consequential or exemplary damages, however arising, even if the company has been advised of the possibility of such damages.

NE- Not Established
< - Less Than
> - Greater Than

INVESTORS AND MEDIA

News Release

<< Back

ISTA Pharmaceuticals Submits New Drug Application for Xibrom(TM) QD (once-daily) 2007

IRVINE, Calif., Dec. 20 /PRNewswire-FirstCall/ -- ISTA Pharmaceuticals, Inc. (Nasdaq: ISTA), announced today the Company has submitted a New Drug Application (NDA) to the U.S. Food and Drug Administration (FDA) for Xibrom(TM) QD (once-daily). The Company is seeking approval for Xibrom QD as a treatment for inflammation, pain, and photophobia following cataract surgery.

Xibrom(TM) (bromfenac ophthalmic solution)

Xibrom is a topical non-steroidal anti-inflammatory compound for the treatment of ocular inflammation and pain. Xibrom, approved in 2005, is the first and only FDA-approved twice-daily NSAID for inflammation and reduction of pain following cataract surgery. Xibrom is the fastest growing ophthalmic product in 2007, according to IMS data. Xibrom, under a different trade name but identical formulation, was launched in Japan in 2000 by Senju Pharmaceuticals Co. Ltd. ISTA acquired U.S. marketing rights for Xibrom in 2002 and launched the product in the U.S. in 2005.

ABOUT ISTA PHARMACEUTICALS

ISTA Pharmaceuticals is an ophthalmic pharmaceutical company. ISTA's products and product candidates addressing the $3.2 billion U.S. prescription ophthalmic industry include therapies for inflammation, ocular pain, glaucoma, allergy, and dry eye. The Company currently markets three products and is developing a strong product pipeline to fuel future growth and market share. The Company's product development and commercialization strategy is to launch a new product every 12 to 18 months, thereby continuing its growth to become the leading niche ophthalmic pharmaceutical company in the U.S. For additional information regarding ISTA, please visit ISTA Pharmaceuticals' website at http://www.istavision.com.

SOURCE ISTA Pharmaceuticals, Inc.

CONTACT: Vince Anido, +1-949-788-5311, vanido@istavision.com, or Investors, Lauren Silvernail, +1-949-788-5302, lsilvernail@istavision.com, both of ISTA Pharmaceuticals; Media, Justin Jackson, jjackson@burnsmc.com, or Investors, Juliane Snowden, +1-212-213-0006, jsnowden@burnsmc.com, both of Burns McClellan, for ISTA Pharmaceuticals

APPENDIX D

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of	:	**Confirmation No. 1756**
Shirou SAWA et al.	:	Attorney Docket No. 2005_0232A
Serial No. 10/525,006	:	Group Art Unit 1614
Filed March 28, 2005	:	Examiner Timothy P. Thomas
AQUEOUS LIQUID PREPARATION CONTAINING 2-AMINO-3-(4-BROMOBENZOYL)PHENYLACETIC ACID	:	**Mail Stop: Amendment**

THE COMMISSIONER IS AUTHORIZED TO CHARGE ANY DEFICIENCY IN THE FEES FOR THIS PAPER TO DEPOSIT ACCOUNT NO 23-0975

INFORMATION DISCLOSURE STATEMENT

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

Sir:

Pursuant to the provisions of 37 CFR 1.56, 1.97 and 1.98, Applicants request consideration of the references listed on attached form PTO-1449 and any additional information identified below in paragraph 3. A legible copy of each reference listed on the Form PTO-1449 is enclosed, except a copy is not provided for:

[X] each U.S. Patent and U.S. Patent application publication;

[] each reference previously cited in the international application PCT/_____; and/or

[] each reference previously cited in prior parent application Serial No. _____.

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 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, 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.

3. [] Consideration of the following list of additional information (including any copending or abandoned U.S. application, prior uses and/or sales, etc.) is requested.

4. For each non-English language reference listed on the attached form PTO-1449, reference is made to:

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

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

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

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

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

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

6. [] Statement Under 37 CFR 1.704(d)

   Each item of information contained in the Information Disclosure Statement was first cited in any communication from a foreign Patent Office in a counterpart application, 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,

Shirou SAWA et al.

By _____
Warren M. Cheek
Registration No. 33,367
Attorney for Applicants

WMC/dlk
Washington, D.C. 20006-1021
Telephone (202) 721-8200
Facsimile (202) 721-8250
March 26, 2008

Sheet 1 of 1

INFORMATION DISCLOSURE STATEMENT

FORM PTO 1449 (*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: March 26, 2008

ATTY DOCKET NO.	SERIAL NO.
2005_0232A	10/525,006

APPLICANT	
Shirou SAWA et al.	

FILING DATE	GROUP
March 28, 2005	1614

U.S. PATENT DOCUMENTS

*EXAMINER INITIAL		DOCUMENT NUMBER	DATE	NAME	CLASS	SUBCLASS	FILING DATE IF APPROPRIATE
	AA						
	AB						
	AC						
	AD						
	AE						
	AF						
	AG						
	AH						
	AI						

FOREIGN PATENT DOCUMENTS

		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION YES	TRANSLATION NO
	BA							
	BB							
	BC							
	BD							
	BE							

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

	CA	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.
	CB	Complete English translation of New Drugs in Japan, 2001, 2001 Edition, Published by Yakuji Nippo Ltd., May 11, 2001, pp. 27-29.
	CC	

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	:	**Confirmation No. 1756**
Shirou SAWA et al.	:	Attorney Docket No. 2005_0232A
Serial No. 10/525,006	:	Group Art Unit 1614
Filed March 28, 2005	:	Examiner Timothy P. Thomas

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

Mail Stop AMENDMENT

THE COMMISSIONER IS AUTHORIZED TO CHARGE ANY DEFICIENCY IN THE FEES FOR THIS PAPER TO DEPOSIT ACCOUNT NO 23-0975

PATENT OFFICE FEE TRANSMITTAL FORM

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

Sir:

Attached hereto is a check in the amount of **$2,450.00** to cover Patent Office fees relating to filing the following attached papers:

Petition for Extension of Time **$1,050.00**

Additional Claims Fee Transmittal Letter
Excess of Twenty **$800.00**
Independent **$420.00**
Multiple Dependent Fee ..... **$**
IDS... ..... **$180.00**

A duplicate copy of this paper is being submitted for use in the Accounting Division, Office of Finance.

The Commissioner is authorized to charge any deficiency or to credit any overpayment associated with this communication to Deposit Account No. 23-0975, with the EXCEPTION of deficiencies in fees for multiple dependent claims in new applications.

Respectfully submitted,
Shirou SAWA et al.

By: Warren M. Cheek
Warren M. Cheek
Registration No. 33,367
Attorney for Applicants

WMC/dlk
WENDEROTH, LIND & PONACK, L.L.P.
2033 K St., N.W., Suite 800
Washington, D.C. 20006-1021
Telephone (202) 721-8200
March 26, 2008

[Check No. 85361]

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of	:	**Confirmation No. 1756**
Shirou SAWA et al.	:	Attorney Docket No. 2005_0232A
Serial No. 10/525,006	:	Group Art Unit 1614
Filed March 28, 2005	:	Examiner Timothy P. Thomas

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

Mail Stop: Amendment

THE COMMISSIONER IS AUTHORIZED TO CHARGE ANY DEFICIENCY IN THE FEES FOR THIS PAPER TO DEPOSIT ACCOUNT NO 23-0975

PETITION FOR EXTENSION OF TIME

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

Sir:

Petition hereby is made for a three month extension of time to respond to the communication of September 27, 2007.

The fee of $1,050.00 is
(X) submitted herewith.
() to be charged to Deposit Account No. 23-0975. A duplicate copy of this Petition is enclosed.

() Small entity status of this application is established by a Small Entity Status Assertion which
- () is enclosed.
- () has been previously submitted.
- () has been previously asserted.

Respectfully submitted,

Shirou SAWA et al.

By _____
Warren M. Cheek
Registration No. 33,367
Attorney for Applicants

03/31/2008 LLANDGRA 00000061 10525006
01 FC:1253 1050.00 OP

WMC/dlk
Washington, D.C. 20006-1021
Telephone (202) 721-8200
Facsimile (202) 721-8250
March 26, 2008

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
10/525,006	03/28/2005	

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY ☐ RATE ($)	SMALL ENTITY ☐ FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =		OR	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =			X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT 03/26/2008	(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))	* 45	Minus	** 22	= 23	X $ =		OR	X $50=	1150
Independent (37 CFR 1.16(h))	* 7	Minus	***3	= 4	X $ =		OR	X $210=	840
☐ 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	1990

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:
/GOIGA N. DUCKETT/

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.
10/525,006	03/28/2005	Shirou Sawa	2005_0232A	1756

513 7590 03/20/2008

WENDEROTH, LIND & PONACK, L.L.P.
2033 K STREET N. W.
SUITE 800
WASHINGTON, DC 20006-1021

EXAMINER	
THOMAS, TIMOTHY P	

ART UNIT	PAPER NUMBER
1614	

MAIL DATE	DELIVERY MODE
03/20/2008	PAPER

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.

Interview Summary	Application No.	Applicant(s)	
	10/525,006	SAWA ET AL.	
	Examiner	Art Unit	
	TIMOTHY P. THOMAS	1614	

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

(1) *TIMOTHY P. THOMAS*. (3)*Warren Cheek*.

(2) *Ardin Marschel*. (4)_____.

Date of Interview: *13 March 2008*.

Type: a)☐ Telephonic b)☐ Video Conference
c)☒ Personal [copy given to: 1)☐ applicant 2)☐ applicant's representative]

Exhibit shown or demonstration conducted: d)☐ Yes e)☒ No.
If Yes, brief description: _____.

Claim(s) discussed: *19 and 20*.

Identification of prior art discussed: *See Continuation Sheet*.

Agreement with respect to the claims f)☐ was reached. g)☒ was not reached. h)☐ N/A.

Substance of Interview including description of the general nature of what was agreed to if an agreement was reached, or any other comments: *the objection to the oath and rejections under 35 USC 102 and 103 were discussed with possible claim amendments that might be adopted. See attached 892 and copy of reference.*.

(A fuller description, if necessary, and a copy of the amendments which the examiner agreed would render the claims allowable, if available, must be attached. Also, where no copy of the amendments that would render the claims allowable is available, a summary thereof must be attached.)

THE FORMAL WRITTEN REPLY TO THE LAST OFFICE ACTION MUST INCLUDE THE SUBSTANCE OF THE INTERVIEW. (See MPEP Section 713.04). If a reply to the last Office action has already been filed, APPLICANT IS GIVEN A NON-EXTENDABLE PERIOD OF THE LONGER OF ONE MONTH OR THIRTY DAYS FROM THIS INTERVIEW DATE, OR THE MAILING DATE OF THIS INTERVIEW SUMMARY FORM, WHICHEVER IS LATER, TO FILE A STATEMENT OF THE SUBSTANCE OF THE INTERVIEW. See Summary of Record of Interview requirements on reverse side or on attached sheet.

/Timothy P. Thomas/
Patent Examiner
Examiner's signature, if required

Examiner Note: You must sign this form unless it is an Attachment to a signed Office action.

Summary of Record of Interview Requirements

Manual of Patent Examining Procedure (MPEP), Section 713.04, Substance of Interview Must be Made of Record
A complete written statement as to the substance of any face-to-face, video conference, or telephone interview with regard to an application must be made of record in the application whether or not an agreement with the examiner was reached at the interview.

Title 37 Code of Federal Regulations (CFR) § 1.133 Interviews
Paragraph (b)

In every instance where reconsideration is requested in view of an interview with an examiner, a complete written statement of the reasons presented at the interview as warranting favorable action must be filed by the applicant. An interview does not remove the necessity for reply to Office action as specified in §§ 1.111, 1.135. (35 U.S.C. 132)

37 CFR §1.2 Business to be transacted in writing.
All business with the Patent or Trademark Office should be transacted in writing. The personal attendance of applicants or their attorneys or agents at the Patent and Trademark Office is unnecessary. The action of the Patent and Trademark Office will be based exclusively on the written record in the Office. No attention will be paid to any alleged oral promise, stipulation, or understanding in relation to which there is disagreement or doubt.

The action of the Patent and Trademark Office cannot be based exclusively on the written record in the Office if that record is itself incomplete through the failure to record the substance of interviews.

It is the responsibility of the applicant or the attorney or agent to make the substance of an interview of record in the application file, unless the examiner indicates he or she will do so. It is the examiner's responsibility to see that such a record is made and to correct material inaccuracies which bear directly on the question of patentability.

Examiners must complete an Interview Summary Form for each interview held where a matter of substance has been discussed during the interview by checking the appropriate boxes and filling in the blanks. Discussions regarding only procedural matters, directed solely to restriction requirements for which interview recordation is otherwise provided for in Section 812.01 of the Manual of Patent Examining Procedure, or pointing out typographical errors or unreadable script in Office actions or the like, are excluded from the interview recordation procedures below. Where the substance of an interview is completely recorded in an Examiners Amendment, no separate Interview Summary Record is required.

The Interview Summary Form shall be given an appropriate Paper No., placed in the right hand portion of the file, and listed on the "Contents" section of the file wrapper. In a personal interview, a duplicate of the Form is given to the applicant (or attorney or agent) at the conclusion of the interview. In the case of a telephone or video-conference interview, the copy is mailed to the applicant's correspondence address either with or prior to the next official communication. If additional correspondence from the examiner is not likely before an allowance or if other circumstances dictate, the Form should be mailed promptly after the interview rather than with the next official communication.

The Form provides for recordation of the following information:
- Application Number (Series Code and Serial Number)
- Name of applicant
- Name of examiner
- Date of interview
- Type of interview (telephonic, video-conference, or personal)
- Name of participant(s) (applicant, attorney or agent, examiner, other PTO personnel, etc.)
- An indication whether or not an exhibit was shown or a demonstration conducted
- An identification of the specific prior art discussed
- An indication whether an agreement was reached and if so, a description of the general nature of the agreement (may be by attachment of a copy of amendments or claims agreed as being allowable). Note: Agreement as to allowability is tentative and does not restrict further action by the examiner to the contrary.
- The signature of the examiner who conducted the interview (if Form is not an attachment to a signed Office action)

It is desirable that the examiner orally remind the applicant of his or her obligation to record the substance of the interview of each case. It should be noted, however, that the Interview Summary Form will not normally be considered a complete and proper recordation of the interview unless it includes, or is supplemented by the applicant or the examiner to include, all of the applicable items required below concerning the substance of the interview.

A complete and proper recordation of the substance of any interview should include at least the following applicable items:

1) A brief description of the nature of any exhibit shown or any demonstration conducted,
2) an identification of the claims discussed,
3) an identification of the specific prior art discussed,
4) an identification of the principal proposed amendments of a substantive nature discussed, unless these are already described on the Interview Summary Form completed by the Examiner,
5) a brief identification of the general thrust of the principal arguments presented to the examiner,
   (The identification of arguments need not be lengthy or elaborate. A verbatim or highly detailed description of the arguments is not required. The identification of the arguments is sufficient if the general nature or thrust of the principal arguments made to the examiner can be understood in the context of the application file. Of course, the applicant may desire to emphasize and fully describe those arguments which he or she feels were or might be persuasive to the examiner.)
6) a general indication of any other pertinent matters discussed, and
7) if appropriate, the general results or outcome of the interview unless already described in the Interview Summary Form completed by the examiner.

Examiners are expected to carefully review the applicant's record of the substance of an interview. If the record is not complete and accurate, the examiner will give the applicant an extendable one month time period to correct the record.

Examiner to Check for Accuracy

If the claims are allowable for other reasons of record, the examiner should send a letter setting forth the examiner's version of the statement attributed to him or her. If the record is complete and accurate, the examiner should place the indication, "Interview Record OK" on the paper recording the substance of the interview along with the date and the examiner's initials.

Continuation of Identification of prior art discussed: Gamache, et al. (WO 01/15677 A2); Dobrozsi (US 6,319,513 B1); Sawa (US 2007/0082857 A1); ISTA Pharmaceuticals ("New Drug Applications: Xibrom"; http://www.drugs.com/nda/xibrom_040525.html; accessed 9/19/2007); Nolan, et al. (Agents and Actions; 25 (1-2): 77-85, abstract); Yakuji Nippo Ltd ("New Drugs in Japan", 2001, IDS reference AP, English section translation); Xia (US 6,369,112 B1).

.

Notice of References Cited	Application/Control No. 10/525,006	Applicant(s)/Patent Under Reexamination SAWA ET AL.	
	Examiner TIMOTHY P. THOMAS	Art Unit 1614	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
	A	US-			
	B	US-			
	C	US-			
	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					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	Nolan, et al. ("The topicla anti-inflammatory and analgesic properties of bromfenac in rodents"; 1988; Agents and Actions; 25(1-2): 77-85
	V	
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

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.
10/525,006	03/28/2005	Shirou Sawa	2005_0232A	1756

513 7590 09/27/2007

WENDEROTH, LIND & PONACK, L.L.P.
2033 K STREET N. W.
SUITE 800
WASHINGTON, DC 20006-1021

EXAMINER	
THOMAS, TIMOTHY P	

ART UNIT	PAPER NUMBER
1614	

MAIL DATE	DELIVERY MODE
09/27/2007	PAPER

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.

Office Action Summary	Application No.	Applicant(s)	
	10/525,006	SAWA ET AL.	
	Examiner	Art Unit	
	Timothy P. Thomas	1614	

-- 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 *20 August 2007*.

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

3)☐ 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

4)☒ Claim(s) *19-40* is/are pending in the application.

4a) Of the above claim(s) *39 and 40* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *19-38* is/are rejected.

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

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

Application Papers

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

10)☐ 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).

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

Priority under 35 U.S.C. § 119

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) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *See Continuation Sheet*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Attachment(s) 3). Information Disclosure Statement(s) (PTO/SB/08), Paper No(s)/Mail Date :2/17/2005, 4/11/2005, 7/12/2007.

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of group I, claims 19-38 in the reply filed on 8/20/2007 is acknowledged.

2. Applicant's election without traverse of claim 20 as the alkyl aryl polyether alcohol type polymer or polyethylene glycol fatty acid ester species (interpreted as tyloxapol, contained in the claim) in the reply filed on 8/20/2007 is acknowledged.

3. Claims 39-40 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 8/20/2007.

Status of Claims

4. Claims 19-40 are pending. Claims 39-40 are withdrawn. Claims 19-38 are examined on the basis of the merits.

Priority

5. Applicant is advised of possible benefits Applicant is advised of possible benefits under 35 U.S.C. 119(a)-(d), wherein an application for patent filed in the United States may be entitled to the benefit of the filing date of a prior application filed in a foreign country.

6. Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

Acknowledgement is made of applicant's claim to foreign priority and the receipt of a copy of the application, JP2003-012427, filed 1/21/2003. However, since no

translation has been provided, prior art dates have been determined with reference to the priority date for the PCT application date, PCT/JP04/00350, filed 1/16/2004.

Oath/Declaration

7. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:
It was not executed in accordance with either 37 CFR 1.66 or 1.68.

The oath or declaration contains no signatures of the inventors with date signed

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

9. Claims 19-24 and 31 are rejected under 35 U.S.C. 102(b) as being anticipated by Gamache, et al. (WO 01/15677 A2; 03/2001).

Gamache teaches all of the components of the claims: 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 (the first compound of instant claim 19; claim 11;); 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 at the concentration of 0.05 % (w/v) (p. 16, line 30). It is noted that claim 21 and further dependent claims limit the options for the salt of bromfenac to the sodium salt, and that the specific concentrations recited in dependent claims apply to the sodium salt; the other options (bromfenac or a hydrate of bromfenac) are still viable choices that are part of the claims 21 and dependent claims (which depend on and include the options of claim 20). Gamache anticipates 1) the claim to bromfenac in the concentration range of claim 20 (which is also an option of claims 21-24 and 31). 2) The 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; for this case Gamache also anticipates the sodium salt limitation of claim 21, albeit not the sodium salt concentration limitation of claim 22 and further dependent claims, since the claim is drawn to an aqueous liquid preparation, irrespective of how it is prepared.

10. Claim 19 is rejected under 35 U.S.C. 102(b) as being anticipated by Dobrozsi (US 6,319,513 B1; 11/2001).

Dobrozsi teaches aqueous liquid compositions comprising a pharmaceutically active agent selected from a group that includes analgesics (abstract); a specie taught is bromfenac (column 10, line 11); tyloxapol is taught at 0.15 and 0.035 % (Example 10).

11. Claims 19-38 are rejected under 35 U.S.C. 102(e) as being anticipated by Sawa (US 2007/0082857 A1; priority date 11/2003).

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

Sawa teaches the elements of the claims: aqueous solution preparations comprising an aminoglycoside antibiotic and bromfenac or a salt of bromfenac (abstract); bromfenac sodium and bromfenac sodium hydrate is taught at 0.1 and 0.2 % (Tables 1, 3, 6, 9-15); tyloxapol at 0.3 % resulted in solutions that were clear, when the control (no additive) was turbid (Table 5, 8), tyloxapol is also taught at 0.02 % (Table 15); additives taught include benzalkonium chloride (Table 8), boric acid (Tables 9, 12), sodium edentate (Table 15), and sodium hydroxide (Table 15); pH values include 7.5, 7.8 and 8.0 (Tables 9-15); eye drop formulations are also taught (Examples 1-7). It is noted that the aqueous preparations contain an active ingredient not in the instant

claims. However, Sawa still anticipates the instant claims, due to the open language construction of the claims (use of "comprising").

12. Applicant cannot rely upon the foreign priority papers to overcome this rejection because a translation of said papers has not been made of record in accordance with 37 CFR 1.55. See MPEP § 201.15.

Claim Rejections - 35 USC § 103

13. 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.

14. 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.

15. 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).

16. Claims 19-29, 31-34, and 36-38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gamache, et al. (WO 01/15677 A2; 03/2001) and ISTA Pharmaceuticals ("New Drug Applications: Xibrom", http://www.drugs.com/nda/xibrom_040525.html, accessed online 9/19/2007) or Nolan, et al. ("The topical anti-inflammatory and analgesic properties of bromfenic in rodents:; Agents and Actions; 1988 Aug; 25(1-2):77-85, abstract).

Claims 19-24 and 31 are rejected as outlined above. With respect to claims 21-38 (claims 21-24 and 31, with respect to the sodium salt of bromfenic and associated concentrations), in addition to the points made above, Gamache also teaches the additives and pH of the instant claims, edetate disodium, benzylalkonium chloride, sodium hydroxide, and a pH of 7.3-7.4 (Example 2); polyvinyl pyrrolidone (p. 14, line 5); and sodium borate buffer (p. 13, line 11). Gamache does not specifically teach the sodium salt of bromfenic, nor a hydrate, nor the concentration range or specific bromfenic sodium concentrations of 0.05-0.2, or at 0.1 or 0.2 %, nor the tyloxapol concentrations of 0.02 or 0.3 %. The ISTA Pharmaceuticals news release demonstrates that products containing 0.1 % bromfenac sodium acquired US marketing rights for Xibrom in May 2002 (were known by others in this country before applicant's priority date, a 35 USC 102(a) date). Nolan teaches bromfenac (the sodium salt, sesquihydrate form) was effective as a topical analgesic at concentrations of 0.1-0.32 % in mice and more potent than the other drugs tested (abstract). It would have been

obvious for one of ordinary skill in the art at the time of the invention to select concentrations of bromfenac sodium, sesquihydrate of 0.1, about 0.2 and about 0.32 %, in the invention of Gamache, since these values have demonstrated efficacy for topical use. 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, bromfenic, in a more aqueous soluble ionic form. The motivation would have been to prepare pharmaceutical products with optimal drug dosage and stability.

17. Claims 19-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yakuji Nippo Ltd. ("New Drugs in Japan"; 2001; English translation provided; IDS Reference AP) and Xia (US 6,369,112 B1).

Yakuji Nippo teaches a bromfenac sodium sesquihydrate ophthalmic formulation that contains: 0.1% (w/v) bromfenac (items 1-3); boric acid buffer, sodium sulfite, disodium eentate, polyvinylpyrrolidone, and benzalkonium chloride (item 2, additives); a pH of 8.0-8.6 (item 2, pH). Yakuji Nippo does not teach tyloxapol. Xia teaches a solution useful for contact lenses that provides enhanced cleaning and disinfecting efficacy of the contact lens (abstract), which contains tyloxapol as one of three ingredients (abstract; column 3, lines 7-21); tyloxapol is taught at concentrations of 0.25 and 0.025 (about 0.02 and 0.3; Table 1). Xia teaches the addition of tyloxapol to the solution improves the stability and therefore the disinfecting efficacy over time of the

active component (column 7, lines 8-18). It would have been obvious to one of ordinary skill in the art at the time of the invention to add tyloxapol to the ophthalmic formulation of Yakuji Nippo. The motivation to do so is that taught by Xia, the stability enhancing effect of this component on the active ingredient. There would have been an expectation of success, since tyloxapol has demonstrated efficacy with the contact lens cleaning solutions.

18. Claim19-38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yakuji Nippo Ltd. ("New Drugs in Japan"; 2001; English translation provided; IDS Reference AP) and Xia (US 6,369,112 B1) as applied to claims 19-30 above, and further in view of Nolan, et al. ("The topical anti-inflammatory and analgesic properties of bromfenic in rodents:; Agents and Actions; 1988 Aug; 25(1-2):77-85, abstract).

Neither Yakuji Nippo or Xia teach the bromfenac sodium hydrate solutions at a bromfenac concentration of 0.2 %. Nolan teaches topical solutions are efficacious in the concentration range of 0.1-0.32 %. It would have been obvious to one of ordinary skill in the art at the time of the invention to use a concentration of about 0.2% bromfenic sodium hydrate (right in the middle of the range Nolan teaches is effective), in the modified Yakuji Nippo ophthalmic solution with tyloxapol added. The motivation to use a higher bromfenac concentration would be to provide an option of a more concentrated solution for patients in cases where a physician determines that higher anti-inflammatory concentration is desirable, such as when the lower dosage does not completely relieve the inflammation or pain.

Double Patenting

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

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

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

20. Claims 19-38 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-43 of copending Application No. 11/755662. Although the conflicting claims are not identical, they are not patentably distinct from each other because the copending application contains claims drawn to method of treating pain and/or inflammation associated with an ocular condition, by administering the aqueous solutions of the instant claims. It would have been obvious to one of ordinary skill in the art at the time of the invention to use the formulations of the instant claims in the methods of the copending application, since the claims recite that the formulations are eye drops, and the instant abstract also teaches some of the conditions treated of the copending application.

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

Conclusion

21. No claim is allowed.

22. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Timothy P. Thomas whose telephone number is (571) 272-8994. The examiner can normally be reached on Monday-Thursday 6:30 a.m. - 5:00 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on (571) 272-0718. 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.

/TPT/

Timothy P. Thomas
Patent Examiner

9/22/07
ARDIN H. MARSCHEL
SUPERVISORY PATENT EXAMINER

Sheet 1 of 1 | INFORMATION DISCLOSURE STATEMENT | DT12 Rec'd PCT/PTO 17 FEB 2005

FORM PTO 1449 (*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: February 17, 2005

ATTY DOCKET NO.	SERIAL NO.
2005_0232A	NEW 10/525006

APPLICANT	
Shirou SAWA et al.	

FILING DATE	GROUP
February 17, 2005	

U.S. PATENT DOCUMENTS

*EXAMINER INITIAL		DOCUMENT NUMBER	DATE	NAME	CLASS	SUBCLASS	FILING DATE IF APPROPRIATE
	AA						
	AB						
	AC						
	AD						

FOREIGN PATENT DOCUMENTS

		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION YES	TRANSLATION NO
	AE	9-503791	4/1997	JP				
	AF	2-124817	5/1990	JP				
	AG	1-104023	4/1989	JP				
	AH	00/59475	10/2000	WO				
	AI	11-228404	8/1999	JP	copies not provided			
	AJ							
	AK							
	AL							

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

	AM	
	AN	
	AO	

EXAMINER	/Timothy Thomas/	DATE CONSIDERED	09/19/2007

*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 form with next communication to applicant.

Sheet 1 of 1 | INFORMATION DISCLOSURE STATEMENT

FORM PTO 1449 (*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: April 11, 2005

ATTY DOCKET NO.	SERIAL NO.
2005_0232A	11/525,006
APPLICANT	
Shirou SAWA et al.	
FILING DATE	**GROUP**
February 17, 2005	

U.S. PATENT DOCUMENTS

*EXAMINER INITIAL		DOCUMENT NUMBER	DATE	NAME	CLASS	SUBCLASS	FILING DATE IF APPROPRIATE
/T.P.T./	AA	5,603,929	2/1997	Desai et al.			Corresponds to Ref AH
	AB	5,653,972	8/1997	Desai et al.			Corresponds to Ref AH
	AC	4,910,225	3/1990	Ogawa et al.			Corresponds to Ref AI
	AD	5,110,493	5/1992	Cherng-Chyi et al.			Corresponds to Ref AJ
	AE	6,383,471	5/2002	Chen et al.			Corresponds to Ref AK
	AF	4,045,576	8/1977	Welstead, Jr. et al.			Corresponds to Ref AM
	AG	4,683,242	7/1987	Poser			Corresponds to Ref AN

FOREIGN PATENT DOCUMENTS

		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION YES NO.
	AH	9-503791	4/1997	JP			
	AI	2-124817	5/1990	JP			
	AJ	1-104023	4/1989	JP			
	AK	00/59475	10/2000	WO	copies not provided		
/T.P.T./	AL	11-228404	8/1999	JP			Yes
/T.P.T./	AM	5-223052	8/1993	JP			Abstract
	~~AN~~	~~62-126124~~	~~6/1987~~	~~JP~~	not in English		No
	AO						

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

/T.P.T./	AP	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.
	AQ	

EXAMINER	/Timothy Thomas/	DATE CONSIDERED	09/19/2007

*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.