AO 120 (Rev. 08/10)

TO:	REPORT ON THE FILING OR DETERMINATION OF AN ACTION REGARDING A PATENT OR TRADEMARK
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In Compliance with 35 U.S.C. § 290 and/or 15 U.S.C. § 1116 you are hereby advised that a court action has been filed in the U.S. District Court for the District of Delaware on the following

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

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

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

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

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

DATE INCLUDED	INCLUDED BY ☐ Amendment ☐ Answer ☐ Cross Bill ☐ Other Pleading	
PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1		
2		
3		
4		
5		

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

DECISION/JUDGEMENT

CLERK	(BY) DEPUTY CLERK	DATE

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

Trials@uspto.gov
571-272-7822

Paper: 19
Entered: February 19, 2015

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

METRICS, INC., MAYNE PHARMA, and JOHNSON MATTHEY, INC.,
Petitioner,

v.

SENJU PHARMACEUTICAL CO., LTD., BAUSCH & LOMB, INC., and
BAUSCH & LOMB PHARMA HOLDINGS CORP.,
Patent Owner.

Case IPR2014-01041
Patent 8,129,431 B2

Before FRANCISCO C. PRATS, ERICA A. FRANKLIN, and
GRACE KARAFFA OBERMANN, *Administrative Patent Judges.*

OBERMANN, *Administrative Patent Judge.*

DECISION
Instituting *Inter Partes* Review
37 C.F.R. § 42.108

I. BACKGROUND

Petitioner requests an *inter partes* review of claims 1–22 of U.S. Patent No. 8,129,431 B2 (Ex. 1001, "the '431 patent"). Paper 9 ("Pet."). Patent Owner filed a Preliminary Response. Paper 13 ("Prelim. Resp."). We have jurisdiction under 35 U.S.C. § 314(a), which provides that an *inter*

partes review may be instituted upon a showing of "a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition." Petitioner makes that showing with respect to claims 1–22; therefore, we institute review as to those claims.

We authorized, and the parties filed, additional briefing on the issue whether the Petition identifies all real parties-in-interest as required by 35 U.S.C. § 312(a)(2). Paper 15 ("Pet. Opp."); Paper 17 ("PO Reply").

Our findings of fact and conclusions of law, including those relating to the Petition's identification of all real parties-in-interest, are based on the record developed thus far, prior to Patent Owner's Response. This is not a final decision as to the patentability of any challenged claim. Our final decision will be based on the full record developed during trial.

A. Related Proceedings

The '431 patent is the subject of two district court actions. *Senju Pharmaceutical Co. v. Lupin, Ltd.*, C.A. No. 1:14-CV-00667-MAS-LHG (D.N.J.); *Senju Pharmaceutical Co. v. Metrics, Inc*, C.A. No. 1:14-cv-03962-JBS-KMW (D.N.J.); *see* Pet. 12.

Concurrently herewith, we issue a decision to institute in IPR2014-01043, involving the same parties and directed to U.S. Patent No. 8,669,290 B2, which claims priority to the '431 patent.

B. The '431 Patent

The '431 patent relates to an aqueous liquid preparation consisting essentially of two components: (1) bromfenac (or its salts and hydrates); and (2) tyloxapol. Ex. 1001, 11:66–12:10 (independent claim 1). Bromfenac is a non-steroidal anti-inflammatory drug ("NSAID") and tyloxapol serves as a non-ionic surfactant, or stabilizer, in the preparation

recited in the challenged claims. *Id.* at 1:24–47, 2:34–49, 4:37–41. The '431 patent discloses a preparation useful for ophthalmic administration, such as an eye drop to treat blepharitis, conjunctivitis, scleritis, and postoperative inflammation. Ex. 1001, Abstract. The '431 patent discloses that the preparation also is useful as a nasal drop for treatment of allergic rhinitis and inflammatory rhinitis. *Id.*

According to the '431 patent, an object of the invention is to provide an aqueous liquid preparation of bromfenac that "is stable within a pH range giving no irritation to eyes" when preserved with a quaternary ammonium compound, such as benzalkonium chloride ("BAC"). *Id.* at 2:14–22. Petitioner contends, and Patent Owner does not contest at this stage of the proceeding, that NSAIDs were known to interact with BAC to form insoluble complexes, which reduce the stability of the ophthalmic preparation, by rendering the preservative (BAC) less available to serve its function. Pet. 23 (citing Ex. 1003 ¶ 31). The inventors claim to have discovered that addition of an alkyl aryl polyether alcohol type polymer, such as tyloxapol, provides the sought-after stability, giving no irritation to the eyes. Ex. 1001, 2:35–49.

C. Illustrative Claim

Petitioner seeks *inter partes* review of claims 1–22 of the '431 patent. Independent claim 1 is illustrative of the subject matter and is reproduced below.

> 1. An aqueous liquid preparation consisting essentially of the following two components, wherein the first component is 2-amino-3-(4-bromobenzoyl)-phenylaceticacid or a pharmacologically acceptable salt thereof or a hydrate thereof, wherein the hydrate is at least one selected from a 1/2 hydrate, 1 hydrate, and 3/2

> hydrate and the second component is tyloxapol, wherein said liquid preparation is formulated for ophthalmic administration, and wherein when a quaternary ammonium compound is included in said liquid preparation, the quaternary ammonium compound is benzalkonium chloride.

Ex. 1001, 11:66–12:10.

D. Prior Art Relied Upon

Petitioner relies upon the following prior art references:

Owaga, U.S. Patent No. 4,910,225, issued Mar. 20, 1990 (Ex. 1004) ("Owaga").

Sallmann *et al.*, U.S. Patent No. 6,107,343, issued Aug. 22, 2000 (Ex. 1009) ("Sallmann").

Fu, AU-B-22042/88, issued Mar. 16, 1989 (Ex. 1011 ("Fu").

E. The Asserted Grounds of Unpatentability

Petitioner challenges the patentability of claims 1–22 of the '431patent on the grounds set forth in the chart below. *See* Pet. 18–19, 43–46.[1] Petitioner also relies on a declaration of Dr. Uday B. Kompella. Ex. 1003.[2]

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[1] Petitioner's identification of challenged claims in its chart of grounds (Pet. 18–19) differs from the arguments presented in support of the challenges (*see* Pet. 43–46). We identify the challenged claims based on the arguments presented in the Petition.

[2] Dr. Kompella has a Ph.D. in Pharmaceutical Sciences and has significant experience, as a tenured professor, researcher, and author, in the field of ophthalmology and ophthalmic preparations. Ex. 1003 ¶¶ 12–17. He appears on this record to have the requisite familiarity with ophthalmic preparations to opine on the views of a hypothetical person of ordinary skill

References	Basis	Claims Challenged
Owaga and Sallmann	§ 103	1–5, 7–14, and 18–19
Owaga, Sallmann, and Fu	§ 103	6, 15–17, and 20–22

II. ANALYSIS

A. Threshold Issues Under 35 U.S.C. §§ 312 (a)(2), 315(a)(1)

We first address two threshold issues raised by Patent Owner: (1) whether the Petition identifies all real parties-in-interest, as required under 35 U.S.C. § 312(a)(2); and (2) whether Petitioner is barred from pursuing an *inter partes* review under 35 U.S.C. § 315(a)(1).

i. Real Parties-in-Interest under 35 U.S.C. § 312(a)(2)

Patent Owner contends that the filing date of the Petition should be vacated because the Petition does not identify all real parties-in-interest, as required by 35 U.S.C. § 312(a)(2). Prelim. Resp. 14–20. The gravity of that contention, and its potential ramifications, prompted us to authorize further briefing on the issue. We may consider a petition for *inter partes* review only if it identifies all real parties-in-interest. 35 U.S.C. §.312(a)(2).

Patent Owner argues that Coastal Pharmaceuticals, Inc. ("Coastal") is an unidentified real party-in-interest in this proceeding. Prelim. Resp. 1. On that point, Patent Owner contends that Coastal filed, "on [Petitioner's] behalf," a certification with the U.S. Food and Drug Administration ("FDA") pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV) ("Paragraph IV certification"). *Id.* Patent Owner states that Petitioner's "arguments in the

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in the art at the time of the invention. *See id.* At this stage of the proceeding, we find his testimony credible and persuasive.

[P]etition are copies of those in Coastal's Paragraph IV Notice Letter," which "issued [on] the same day by the same counsel" as the Petition. *Id.* at 2; *see id.* at 15–16 (citing Ex. 2001) (comparing pages A-2–A-30 in that letter with pages 1–55 in the Petition). Patent Owner also argues that Petitioner "conceded in district court that [Petitioner] and Coastal are in privity and that any judgment reaching one would reach the other." *Id.* at 2; *see id.* at 16–17 (citing Ex. 2003, 4–5; Ex. 2004, 30–31).

Petitioner responds that Coastal is no more than "a business name" for Petitioner. Pet. Opp. 1. Petitioner argues that its "assumed name" is not a juridical entity apart from Petitioner; therefore, Coastal cannot be considered a separate real party-in-interest. *Id.* at 5 (citing Ex. 1054, "Corporate Certificate of Assumed Name"). In fact, Petitioner comes forward with persuasive evidence that, prior to the filing of the Preliminary Response in this proceeding, counsel for Patent Owner admitted in district court that Coastal and Petitioner are "one and the same" juridical party. *Id.* at 5–6 (citing Ex. 1056, 30:2-23) (transcript of proceeding in New Jersey action).

Petitioner argues, persuasively, "that it would be 'nonsensical' to maintain an action against both a legal entity and its assumed name." Pet. Opp. 8 (citing *Pinkerton's, Inc. v. Superior Court*, 57 Cal. Rptr.2d 356, 360 n.1 (Cal. Ct. App. 1996)). As Petitioner points out, where Samuel Clemens is dismissed from a case, a plaintiff cannot continue to pursue the action against Mark Twain. *Id.* (quoting *Pinkerton's, Inc.*, 57 Cal. Rptr.2d at 357). In fact, because a business name is not a separate juridical entity, the district court in the related New Jersey action "dismissed and terminated the case against Coastal as a d/b/a." *Id.* at 4. "[I]n an effort to promptly resolve this issue," however, Petitioner is amenable to identifying itself as

"Metrics, Inc. d/b/a Coastal Pharmaceuticals" in this proceeding, provided that the Petition retains its original filing date. *Id.*

The evidence of record persuades us that the Petition and the Paragraph IV certification were filed by the same party (namely, Petitioner) on the same day, by the same counsel, and with what appear to be essentially the same arguments—yet Petitioner did not identify the Paragraph IV certification in the Petition. PO Reply 1–2. Although that action, on Petitioner's part, falls short of a model of candor, we are not persuaded that Petitioner was required to identify Coastal as a real party-in-interest in the Petition, based on the evidence presented at this stage of the proceeding.

Petitioner's counsel represents that Coastal is an "assumed name" of Petitioner. Pet. Opp. 5. Petitioner also comes forward with a copy of "a sworn affidavit," which was filed in the related district court litigation, wherein "Stefan Cross, President of Metrics," attests "that Coastal is not a recognized separate entity and is used in the marketplace to distinguish Metrics' contract services business segment from its pharmaceutical products business." Ex. 1055 ¶¶ 12–13; *see* Pet. Opp. 5–6 (quoting Ex. 1056, 30:2–23) (counsel for Petitioner, affirming in district court that Coastal "is not a juridical party, it's not anything other than a trade name").

We agree with Petitioner that "a corporate entity using a business name, or a d/b/a ('doing business as') name, does not create a legal entity in the name" that is "separate from the underlying corporate entity." Pet. Opp. 2; *see id.* at 8 (citing *Snowden v. CheckPoint Check Cashing*, 290 F.3d 631, 634–35 n.2 (4th Cir. 2002); *Pinkerton's, Inc.*, 57 Cal. Rptr.2d at 360 (citing consistent treatment of business names from different jurisdictions)). "The business name is a fiction, and so too is any implication that the business is a

legal entity separate from its owner." *Pinkerton's, Inc.*, 57 Cal. Rptr.2d at 360 (quotations omitted). Accordingly, based on the record developed thus far, we determine that Coastal is not a separate juridical entity or, therefore, a separate real party-in-interest in this proceeding.

Any collateral estoppel effect that arises from our Final Written Decision will bind Petitioner, whether operating as Metrics or under its business name, Coastal. Petitioner, therefore, is not required to file an updated mandatory notice, correcting the real party-in-interest. Based on the information presented thus far, we decline to vacate the filing date accorded the Petition.

ii. Paragraph IV Certification as an "Effective" Declaratory Judgment Action under 35 U.S.C. § 315(a)(1)

Petitioner filed the Paragraph IV certification and, thereby, challenged the validity of the '431 patent prior to the filing of the instant Petition. Prelim. Resp. 12. Patent Owner argues that the filing of that Paragraph IV certification was "the full functional equivalent of initiating a declaratory judgment action and should be viewed as foreclosing" Petitioner's access to an *inter partes* review. Prelim. Resp. 12 (citing 35 U.S.C. § 315(a)(1)). We disagree. Our governing statute states, in relevant part:

> (1) INTER PARTES REVIEW BARRED BY CIVIL ACTION.—An inter partes review may not be instituted if, before the date on which the petition for such a review is filed, the petitioner or real party in interest filed a civil action challenging the validity of a claim of the patent.

35 U.S.C. § 315(a)(1).

When the statute refers to filing a civil action, it refers to filing a complaint with a court to commence a civil action. *See, e.g., Baldwin Cnty. Welcome Ctr. v. Brown*, 466 U.S. 147, 149 (1984) (a civil action is brought

upon filing a complaint with a court); *Ariosa Diagnostics v. Isis Innovation Ltd.*, Case IPR2012-00022, slip op. at 4–5 (PTAB Feb. 12, 2013)(Paper 20) (citing *Baldwin,* 466 U.S. at 149). Petitioner's act of initiating a challenge to patent validity, by filing of a Paragraph IV certification with the FDA, did not involve filing of a complaint with a court. A Paragraph IV certification may represent an out-of-court challenge to patent validity, but it does not constitute "a civil action challenging the validity of" any patent claim. 35 U.S.C. § 315(a). Thus, Petitioner's action of filing a Paragraph IV certification does not bar institution of the present Petition under 35 U.S.C. § 315(a). We have considered, but find unpersuasive, Patent Owner's arguments that a perceived conflict between the America Invents Act and the Hatch-Waxman Act compels a different result. Prelim. Resp. 4–14.

On this record, we determine that the Petition is not time-barred under 35 U.S.C. § 315(a)(1).

B. Claim Construction

In an *inter partes* review, claim terms in an unexpired patent are interpreted according to their broadest reasonable construction in light of the specification of the patent in which they appear. 37 C.F.R. § 42.100(b); Office Patent Trial Practice Guide, 77 Fed. Reg. 48,756, 48,766 (Aug. 14, 2012). Claim terms are given their ordinary and customary meaning, as understood by one of ordinary skill in the art in the context of the entire disclosure. *In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007). If an inventor acts as his or her own lexicographer, the definition must be set forth in the specification with reasonable clarity, deliberateness, and precision. *Renishaw PLC v. Marposs Societa' per Azioni*, 158 F.3d 1243, 1249 (Fed. Cir. 1998). The construction that stays

true to the claim language, and most naturally aligns with the inventor's description, is likely the correct interpretation. *Id.* at 1250.

At this stage of the proceeding, we determine that the claim terms are clear on their face, and none is specially defined in the written description of the '431 patent. No claim term requires express construction for the purposes of this decision. We observe, however, that, notwithstanding Patent Owner's arguments to the contrary, both parties acknowledge that the phrase "consisting essentially of," which appears, for example, in claim 1, has a well-defined meaning in patent law; and that the transitional phrase excludes unrecited ingredients that materially affect the composition. *See, e.g.*, Pet. 3, 14 (correctly stating that definition); Prelim. Resp. 3 (arguing that "the petition misstates or ignores" that transitional phrase); *PPG Indus. Inc. v. Guardian Indus. Corp*, 156 F.3d 1351, 1354 (Fed. Cir. 1998) ("By using the term 'consisting essentially of,' the drafter signals that the invention necessarily includes the listed ingredients and is open to unlisted ingredients that do not materially affect the basic and novel properties of the invention.").

C. The Applied Prior Art

We next turn to the prior art references raised in the Petition and, in particular, to our analysis of what those references convey about the state of the art at the time of the invention of the '431 patent.[3] We discuss facts as

[3] Patent Owner argues that the Petition fails to include "[a] full statement of the reasons for the relief requested," because the Petition advances additional prior art references, outside of those identified in the stated grounds of unpatentability. Prelim. Resp. 37 (quoting 37 C.F.R. § 42.22 (a)(2)); *see id.* at 26 n.4 (citing 37 C.F.R. §§ 42.104(b)(2), (b)(4)). We limit our analysis to "patents or printed publications" identified in the Petition

presented thus far in the record. Any inferences or conclusions drawn from those facts are neither final nor dispositive of any issue.

i. Owaga and Sallmann

Petitioner shows sufficiently that Owaga's Example 6 discloses an aqueous liquid preparation consisting essentially of bromfenac (an NSAID), polysorbate 80 (a non-ionic surfactant), and BAC (a preservative)—and that the liquid preparation is formulated for ophthalmic administration. Pet. 21–22 (claim chart for claim 1); Ex 1004, 10:5–18 (for aqueous liquid preparation), 10:5–9 (for bromfenac and polysorbate 80).

Petitioner also shows sufficiently that Sallmann's Example 2 discloses an aqueous liquid preparation consisting essentially of diclofenac (an NSAID), tyloxapol (a non-ionic surfactant), and BAC (a preservative)—and that the liquid preparation is formulated for ophthalmic administration. Pet. 21–22 (claim chart for claim 1); Ex 1009, 8:1–15 (for aqueous liquid preparation), 8:1–10 (for diclofenac and tyloxapol); Ex. 1003 ¶ 54.

We are persuaded, based on the information presented, that Owaga discloses every element of claim 1, but for the use of tyloxapol as the non-ionic surfactant—Owaga discloses polysorbate 80 for that function. Sallmann, by contrast, discloses every element of claim 1, but for the use of bromfenac as the NSAID—Sallmann discloses diclofenac for that function.

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with particularity for each ground; here, that is a first ground based on Owaga and Sallmann, and a second ground based on Owaga, Sallmann, and Fu. 37 C.F.R. § 42.104(b)(2); *see* 35 U.S. C. § 312 (a petition must identify "with particularity . . . the grounds on which the challenge to each claim is based").

That sets up the central dispute, at this early stage of the proceeding, which is whether Petitioner shows sufficiently that a person of ordinary skill in the art would have been prompted to (1) modify the ophthalmic preparation of Owaga's Example 6, by replacing polysorbate 80 with tyloxapol; or, alternatively, (2) modify the ophthalmic preparation of Sallmann's Example 2, by replacing diclofenac with bromfenac. Either substitution results in a preparation that satisfies every limitation of claim 1.

ii. Fu

The second ground asserted in the Petition relies on Owaga and Sallmann in combination with Fu. Pet. 19, 43–46. Petitioner shows sufficiently that Fu discloses that ophthalmic preparations of NSAIDs and BAC, which contain octylphenols (the class to which tyloxapol belongs) as the non-ionic surfactants, are more stable than those containing polysorbate 80 as the non-ionic surfactant. Ex. 1011, Example 5; Ex. 1003 ¶¶ 33, 64. Fu discloses that the non-ionic surfactant will stabilize an ophthalmic preparation of an NSAID and BAC, when included in a weight-volume percent of 0.02. Ex. 1011, 18:5–28, Example 2, Example 5; Ex. 1003 ¶¶ 75, 93. That disclosure bears upon the dependent claims, which require that "the concentration of the tyloxapol is about 0.02 w/v %." *See, e.g.*, Ex. 1001, 12:33–34 (claim 6), 13:23 (claim 15).

D. Analysis of Grounds of Unpatentability

We next turn to the two asserted grounds of unpatentability, which are based on obviousness over Owaga and Sallmann alone (for claims 1–5, 7–14 and 18–19) and in combination with Fu (for claims 6, 15–17, and 20–22). Pet. 19. Our inferences and conclusions are based on the information presented thus far, and are neither final nor dispositive of any issue. Based

on the information presented in the Petition and the Preliminary Response, we determine that Petitioner is reasonably likely to prevail in showing that (1) claims 1–5, 7–14 and 18–19 are unpatentable over Owaga and Sallmann under 35 U.S.C. § 103; and (2) claims 6, 15–17, and 20–22 are unpatentable over Owaga, Sallmann, and Fu under 35 U.S.C. § 103.

i. Claims 1–5, 7–14 and 18–19 over Owaga and Sallman

Petitioner shows sufficiently that Owaga's Example 6 discloses each element of claim 1, except that Owaga discloses polysorbate 80 as the non-ionic surfactant, whereas claim 1 recites tyloxapol for that function. Pet. 21–22 (claim chart for claim 1, and citations to record therein). Petitioner also shows sufficiently that an ordinary artisan, equipped with the disclosures of Owaga and Sallmann, would have recognized that tyloxapol and polysorbate 80 serve a common function in the art; both are useful as non-ionic surfactants for stabilizing an ophthalmic preparation of an NSAID and BAC. *See* Ex. 1003 ¶¶ 55–58.

In that regard, Sallmann discloses tyloxapol as a preferred non-ionic surfactant in an aqueous ophthalmic preparation of an NSAID and BAC. Ex. 1009, 4:62. Based on the record developed thus far, we are persuaded that, taken together, the disclosures of Owaga and Sallmann would have suggested to an ordinary artisan that either tyloxapol or polysorbate 80 would work to stabilize an ophthalmic preparation of an NSAID and BAC, by preventing the formation of the insoluble complexes that destabilize the preparation. *See* Ex. 1003 ¶¶ 31, 55–58.

A claim likely is obvious if it is no "more than the predictable use of prior art elements according to their established functions," even without an express suggestion to combine. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398,

417 (2007). Where two known alternatives are interchangeable for a desired function, an express suggestion to substitute one for the other is not needed to render a substitution obvious. *In re Fout*, 675 F.2d 297, 301 (CCPA 1982); *In re Siebentritt*, 372 F.2d 566, 568 (CCPA 1967). On this record, Petitioner shows sufficiently that a person of ordinary skill in the art would have expected that substituting tyloxapol, in place of polysorbate 80 in Owaga's Example 6, predictably would result in a stable ophthalmic preparation of bromfenac and BAC.

Patent Owner argues that test results presented in the '290 patent show that polysorbate 80 and tyloxapol, although useful for the common function of stabilizing BAC in a NSAID-containing ophthalmic preparation, nonetheless "were not interchangeable and [] the skilled person would not have substituted one for the other." Prelim. Resp. 28. In that regard, Patent Owner points out that, during patent prosecution, the Office was persuaded that information reflected in Table 1 of the '290 patent establishes "that tyloxapol has an unexpected property in stabilizing an aqueous solution of bromfenac in comparison with polysorbate 80." *Id.* (quoting Ex. 2005, 3–4) (emphasis omitted).

We are not persuaded, however, at this preliminary stage of the proceeding, that Table 1 is probative of secondary considerations of nonobviousness, that is, unexpected results. Ex. 1001, 7:40–55. On this record, the information in Table 1 is insufficient to establish unexpected results, because no comparison is made between the subject matter of the claimed invention and the closest prior art, that is, Owaga or Sallmann. *See* Pet. 51; Ex. 1003 ¶¶ 95–99. A comparison of the information in Table 1 with that in Table 2, moreover, suggests that another factor—a change in pH

from 7.0 in Table 1 to over 8.0 in Table 2—may influence stability. Ex. 1001, 7:40–55 (Table 1, reporting a stability for tyloxapol-containing preparation of 73.8% at pH of 7), 8:16–32 (Table 2, reporting a stability for tyloxapol-containing preparation of over 90% at pH of slightly over 8). Other evidence of record—specifically, Table 11 of Owaga—suggests that the information in Table 1 of the '431 patent, which persuaded the Examiner, is not reliable to establish unexpected results when tyloxapol is selected over polysorbate 80 in a preparation that contains the other elements of claim 1. *See* Ex. 1004, 10:49–52, Table 11 (reporting a stability of 100% for Owaga's Example 6 preparation, formulated with polysorbate 80).

In the alternative, we are persuaded that Petitioner is reasonably likely to prevail in showing that an ordinary artisan would have been led to substitute bromfenac for the diclofenac in the ophthalmic preparation of Sallmann's Example 2. Pet. 26–27 (citing Ex. 1003 ¶ 53); Ex. 1009, 8:1–15 (Sallmann's Example 2, disclosing an ophthalmic preparation that meets every limitation of claim 1, except that Sallmann uses diclofenac and not bromfenac as the NSAID). Sallmann in Example 2 discloses that diclofenac is suitable for use as the NSAID in an ophthalmic preparation of an NSAID and BAC. Ex. 1009, 8:1–15. Owaga in Example 6 discloses that bromfenac is suitable for use as the NSAID in an ophthalmic preparation of an NSAID and BAC. Ex. 1004, 10:5–9. At the time of the invention, bromfenac and diclofenac were known to share several structural features. Pet. 27; Ex. 1003 ¶¶ 24, 27.

Petitioner shows sufficiently that an ordinary artisan, equipped with the disclosures of Sallmann and Owaga, would have expected that diclofenac and bromfenac would work interchangeably in an ophthalmic

preparation of an NSAID and BAC. At this stage of the proceeding, we are persuaded that those disclosures would have led one to modify the preparation of Sallmann's Example 2, by using bromfenac as an interchangeable alternative to diclofenac, because both were known to serve the same function in an ophthalmic preparation. *See KSR Int'l Co.*, 550 U.S. at 417 (a claim likely is obvious if it is no "more than the predictable use of prior art elements according to their established functions").

On this record, Petitioner establishes also a reasonable likelihood of showing that the subject matter of claims 2–5, 7–14 and 18–19 would have been obvious over Owaga and Sallmann. Pet. 31–43, 47–50. Claim 18 is the only independent claim, other than claim 1. Ex. 1001, 13:16–14:9 (claim 18). Petitioner comes forward with evidence adequate to establish that the subject matter of claim 18 would have been obvious over Owaga and Sallmann, for the same reasons discussed above in connection with claim 1. Pet. 31–35. Petitioner also shows sufficiently that the dependent claims "merely recite concentrations or ranges of specific ingredients" that "the '431 patent characterizes as 'conventional.'" Pet. 35 (citing Ex. 1001, 6:11–31). Petitioner advances evidence adequate to establish that the additional features recited in the dependent claims add nothing of patentable consequence. Pet. 36–43, 47–50.

Accordingly, based on the information presented at this preliminary stage of the proceeding, Petitioner is reasonably likely to prevail in showing that claims 1–5, 7–14 and 18–19 are unpatentable over Owaga and Sallmann. Our findings and conclusions are not final and may change upon consideration of the whole record developed during trial.

ii. Claims 6, 15–17, and 20–22 over Owaga, Sallmann, and Fu

Petitioner is reasonably likely to prevail in showing that claims 6, 15–17, and 20–22 are unpatentable over Owaga, Sallmann, and Fu under 35 U.S.C. § 103. Those claims require a concentration of tyloxapol that "is about 0.02 w/v %." *See, e.g.*, Ex. 1001, 12:55 (claim 6); 13:2–3 (claim 15). Based on the record developed at this preliminary stage of the proceeding, we are persuaded the Petitioner comes forward with evidence sufficient to establish that a person of ordinary skill in the art would have been prompted by Fu to include tyloxapol, in a concentration of "about 0.02 w/v %," *id.*, in the modified composition of Owaga or Sallmann. Pet. 44–46.

Specifically, Petitioner shows sufficiently that Fu would have suggested to an ordinary artisan "that ophthalmic formulations of NSAIDs and BAC containing ethyoxylated octylphenols (the class that includes tyloxapol) as the non-ionic surfactant are more stable than those containing polysorbate 80 as the non-ionic surfactant." Pet. 46 (citing Ex. 1011, Example 5; Ex. 1003 ¶¶ 34–35, 75–76); Ex. 1011, 4. Furthermore, Fu suggests using that class of non-ionic surfactants in a concentration of 0.02 w/v % in the modified ophthalmic formulation" suggested by Owaga and Sallmann. *Id.* (citing Ex. 1011, 18:5–28, Example 2, Example 5; Ex. 1003 ¶¶ 75–76).

Moreover, it appears to us, at this stage of the proceeding, that it would have been within the grasp of an ordinary artisan to manipulate the concentration of tyloxapol in the modified preparation of Owaga or Sallmann "to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456–57 (CCPA 1955) ("where the general conditions of a claim are disclosed in the prior art, it is not

inventive to discover the optimum or workable ranges by routine experimentation").

Here again, our findings and conclusions are not final and may change upon consideration of the whole record developed during trial. Based on the information presented at this early stage of the proceeding, however, we are persuaded that Petitioner is reasonably likely to prevail in showing that claims 6, 15–17, and 20–22 are unpatentable over Owaga, Sallmann, and Fu.

E. Patent Owner's Other Arguments

We have considered each counterargument presented in Patent Owner's Preliminary Response. At this early stage of the proceeding, however, none persuades us to deny the Petition. We discuss some of those arguments below, observing that our factual findings and conclusions of law are not final at this preliminary stage of the proceeding.

i. Multiple Proceedings under 35 U.S.C. § 325(d)

We have considered Patent Owner's suggestion that we should exercise our discretion to deny the Petition because it raises substantially the same arguments or prior art that were raised during patent prosecution. Prelim. Resp. 25–37. Patent Owner's arguments and evidence do not persuade us that the Office previously considered or resolved the arguments as to Owaga and Sallmann that are raised in the Petition. *Id.*; Ex. 2005 (evidence of patent prosecution file history). Accordingly, we decline to exercise our discretion to deny the Petition under 35. U.S.C. § 325(d).

ii. Presentation of Alternative Arguments

Patent Owner also contends that the Petition is defective because, for example, as to the ground based on Owaga and Sallmann, the Petition "switches Owaga's order of application, making it a secondary reference to

Sallmann and creating an entirely different alleged ground of unpatentability." Prelim. Resp. 40. We find that argument unpersuasive, where Patent Owner does not show sufficiently any tangible prejudice resulting from what, in our view, amounts to Petitioner's proper presentation of alternative arguments. *See In re Bush*, 296 F.2d 491, 496 (CCPA 1961) ("[T]o term one reference primary and the other secondary" is a distinction "of little consequence, and [] basing arguments on" such distinctions is an attempt 'to make a mountain out of a mole-hill.'") (quotation omitted).

iii. Request to Expunge Hara

Patent Owner objects to Exhibit 1002, which Petitioner advances as an English translation of Hara,[4] on the grounds that Petitioner provides no "affidavit attesting to the accuracy of the translation." Prelim. Resp. 34 (quoting 37 C.F.R. § 42.63(b)). Specifically, Patent Owner requests that we expunge Exhibit 1002 from the record, and reject Petitioner's reliance upon it, for failure to comply with the Board's Rule 42.63(b). *Id.*

We do not consider Hara in our analysis, because it is not identified with particularity as providing a basis for unpatentability in any ground. *See supra* n.3. In any event, based on the record developed thus far, we determine that Patent Owner's request for relief is premature. Within ten (10) business days of the institution of trial, Patent Owner may serve on Petitioner an objection to Exhibit 1002. 37 C.F.R. § 42.64(b)(1). Petitioner may respond to the objection by timely serving supplemental evidence (for example, an affidavit attesting to the accuracy of the translation). *Id.* § 42.64(b)(2). Should a disagreement persist regarding the admissibility of

[4] Yoshiyuki Hara, "Bromfenac sodium hydrate," *Clinics & Drug Therapy* 2000, Vol. 19, No. 10, 19:1014-1015 (2002).

Exhibit 1002, Patent Owner may raise its objections in a timely-filed motion to exclude evidence, which we shall resolve in our Final Written Decision.

III. CONCLUSION

Based on the information presented in the Petition, as well as the arguments and evidence presented in the Preliminary Response, we conclude that Petitioner has demonstrated a reasonable likelihood of prevailing on its assertion that claims 1–22 of the '431 patent are unpatentable. We institute trial based on each ground of unpatentability stated in the Petition. At this preliminary stage of the proceeding, the Board has not made a final determination as to the patentability of any challenged claim.

IV. ORDER

It is:

ORDERED that an *inter partes* review is instituted, as to claims 1–22 of the '431 patent, on the following grounds:

A. Claims 1–5, 7–14, and 18–19 as unpatentable over Owaga and Sallmann under 35 U.S.C. § 103;

B. Claims 6, 15–17, and 20–22 as obvious over Owaga, Sallmann, and Fu;

FURTHER ORDERED that no other ground of unpatentability is authorized; and

FURTHER ORDERED that notice is hereby given of the institution of a trial commencing on the entry date of this decision. 35 U.S.C. § 314(c); 37 C.F.R. §42.4.

PETITIONER:

Patrick McPherson
Duane Morris LLP
pdmcpherson@duanemorris.com

Vincent Capuano
Duane Morris LLP
vcapuano@duanemorris.com

PATENT OWNER:

M. Andrew Holtman
Finnegan, Henderson, Farabow, Garrett & Dunner, LLP
andy.holtman@finnegan.com

Jonathan Stroud
Finnegan, Henderson, Farabow, Garrett & Dunner, LLP
jonathan.stroud@finnegan.com

AO 120 (Rev. 08/10)

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

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

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

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

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

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

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

PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1		
2		
3		
4		
5		

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

DECISION/JUDGEMENT

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

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

AO 120 (Rev. 08/10)

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

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

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

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

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

PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1 US8,129,431 B2	3/6/2012	Senju Pharmaceutical Co., Ltd. - Copy of Complaint included
2 US8,669,290 B2	3/11/2014	Senju Pharmaceutical Co., Ltd.
3 US8,754,131 B2	6/17/2014	Senju Pharmaceutical Co., Ltd.
4		
5		

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

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

DECISION/JUDGEMENT

CLERK	(BY) DEPUTY CLERK	DATE

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

AO 120 (Rev. 08/10)

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

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

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

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

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

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

DECISION/JUDGEMENT

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

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

AO 120 (Rev. 08/10)

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

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

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
3:14–cv–00667–MAS–LHG	1/31/2014	TRENTON, NJ
PLAINTIFF SENJU PHARMACEUTICAL CO., LTD.		DEFENDANT LUPIN, LTD.

PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1 8,129,431	3/6/2012	SENJU PHARMACEUTICAL CO., LTD
2		
3		
4		
5		

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

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

DECISION/JUDGEMENT

CLERK	(BY) DEPUTY CLERK	DATE
William T. Walsh	s/ BETH JONIAK	1/31/2014

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

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
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Alexandria, Virginia 22313-1450
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APPLICATION NO.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/525,006	03/06/2012	8129431	2005_0232A	1756

513 7590 02/15/2012

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

ISSUE NOTIFICATION

The projected patent number and issue date are specified above.

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

The Patent Term Adjustment is 604 day(s). Any patent to issue from the above-identified application will include an indication of the adjustment on the front page.

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

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

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

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

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

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

Authorization for this examiner's amendment was given in a telephone interview with Warren Cheek on December 16, 2011. This application has been amended as follows:

In claim 41, lines 3-4 after a hydrate thereof, **insert** – wherein the hydrate is at least one selected from a 1/2 hydrate, 1 hydrate, and 3/2 hydrate -- .

In claim 64, ~~line 2-3~~ line 3 after a hydrate thereof, **insert** – wherein the hydrate is at least one selected from a 1/2 hydrate, 1 hydrate, and 3/2 hydrate -- .

Change(s) applied to document, /S.G.L./ 1/23/2012

Reasons for Allowance

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

The composition as claimed are found to be patentable over the prior art because the prior art does not teach or fairly suggest an aqueous liquid preparation consisting essentially of the following two components, wherein the first component is 2-amino-3-(4- bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof, and the second component is tyloxapol wherein said liquid preparation is formulated for ophthalmic administration, and wherein when a quaternary ammonium compound is included in said liquid preparation, the quaternary ammonium compound is benzalkonium chloride.

PART B - FEE(S) TRANSMITTAL

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

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

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

513 7590 12/23/2011
WENDEROTH, LIND & PONACK, L.L.P.
1030 15th Street, N.W.,
Suite 400 East
Washington, DC 20005-1503

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

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

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

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/525,006	03/28/2005	Shirou Sawa	2005_0232A	1756

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

APPLN. TYPE	SMALL ENTITY	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	NO	$1740	$300	$0	$2040	03/23/2012

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

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

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

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

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

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

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

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

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

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

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

5. **Change in Entity Status** (from status indicated above)
- ☐ a. Applicant claims SMALL ENTITY status. See 37 CFR 1.27.
- ☐ b. Applicant is no longer claiming SMALL ENTITY status. See 37 CFR 1.27(g)(2).

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

Authorized Signature /Warren M. Cheek/ Originally signed by /Warren M. Cheek/ DN: cn=/Warren M. Cheek/, o, ou, email=wcheek@wenderoth.com, c=US Date: 2012.01.20 10:14:06 -05'00' Date January 20, 2012

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

This collection of information is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

Electronic Patent Application Fee Transmittal

Application Number:	10525006
Filing Date:	28-Mar-2005
Title of Invention:	AQUEOUS LIQUID PREPARATION CONTAINING 2-AMINO-3-(4-BROMOBENZOYL)PHENYLACETIC ACID
First Named Inventor/Applicant Name:	Shirou Sawa
Filer:	Warren M. Cheek Jr./Donna King
Attorney Docket Number:	2005_0232A

Filed as Large Entity

U.S. National Stage under 35 USC 371 Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Utility Appl issue fee	1501	1	1740	1740
Publ. Fee- early, voluntary, or normal	1504	1	300	300

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Miscellaneous:				
			Total in USD ($)	**2040**

Electronic Acknowledgement Receipt

EFS ID:	11883300
Application Number:	10525006
International Application Number:	
Confirmation Number:	1756
Title of Invention:	AQUEOUS LIQUID PREPARATION CONTAINING 2-AMINO-3-(4-BROMOBENZOYL)PHENYLACETIC ACID
First Named Inventor/Applicant Name:	Shirou Sawa
Customer Number:	513
Filer:	Warren M. Cheek Jr./ann leveille
Filer Authorized By:	Warren M. Cheek Jr.
Attorney Docket Number:	2005_0232A
Receipt Date:	20-JAN-2012
Filing Date:	28-MAR-2005
Time Stamp:	15:15:15
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	yes
Payment Type	Credit Card
Payment was successfully received in RAM	$2040
RAM confirmation Number	1811
Deposit Account	230975
Authorized User	CHEEK JR.,WARREN M.

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

Charge any Additional Fees required under 37 C.F.R. 1.492 (National application filing, search, and examination fees)

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

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

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

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

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Issue Fee Payment (PTO-85B)	AttachA.pdf	401968 6f13b40de6fb29a302d7e4afa93a1bf5572240eb	no	1

Warnings:

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

Information:

2	Fee Worksheet (SB06)	fee-info.pdf	32676 bf0df21861c991a67291b86c74900d700615ea6c	no	2

Warnings:

Information:

Total Files Size (in bytes):	434644

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

New Applications Under 35 U.S.C. 111

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

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

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

New International Application Filed with the USPTO as a Receiving Office

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

UNITED STATES PATENT AND TRADEMARK OFFICE

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

NOTICE OF ALLOWANCE AND FEE(S) DUE

513 7590 12/23/2011

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

EXAMINER	
SOROUSH, LAYLA	
ART UNIT	PAPER NUMBER
1627	

DATE MAILED: 12/23/2011

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/525,006	03/28/2005	Shirou Sawa	2005_0232A	1756

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

APPLN. TYPE	SMALL ENTITY	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	NO	$1740	$300	$0	$2040	03/23/2012

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

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

HOW TO REPLY TO THIS NOTICE:

I. Review the SMALL ENTITY status shown above.

If the SMALL ENTITY is shown as YES, verify your current SMALL ENTITY status:

A. If the status is the same, pay the TOTAL FEE(S) DUE shown above.

B. If the status above is to be removed, check box 5b on Part B - Fee(s) Transmittal and pay the PUBLICATION FEE (if required) and twice the amount of the ISSUE FEE shown above, or

If the SMALL ENTITY is shown as NO:

A. Pay TOTAL FEE(S) DUE shown above, or

B. If applicant claimed SMALL ENTITY status before, or is now claiming SMALL ENTITY status, check box 5a on Part B - Fee(s) Transmittal and pay the PUBLICATION FEE (if required) and 1/2 the ISSUE FEE shown above.

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

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

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

PART B - FEE(S) TRANSMITTAL

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

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

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

513 7590 12/23/2011

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

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

Certificate of Mailing or Transmission

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

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

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/525,006	03/28/2005	Shirou Sawa	2005_0232A	1756

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

APPLN. TYPE	SMALL ENTITY	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	NO	$1740	$300	$0	$2040	03/23/2012

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

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

❑ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.

❑ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list

(1) the names of up to 3 registered patent attorneys or agents OR, alternatively,

(2) the name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 _____

2 _____

3 _____

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

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

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

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

4a. The following fee(s) are submitted:

❑ Issue Fee

❑ Publication Fee (No small entity discount permitted)

❑ Advance Order - # of Copies _____

4b. Payment of Fee(s): **(Please first reapply any previously paid issue fee shown above)**

❑ A check is enclosed.

❑ Payment by credit card. Form PTO-2038 is attached.

❑ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment, to Deposit Account Number _____ (enclose an extra copy of this form).

5. **Change in Entity Status** (from status indicated above)

❑ a. Applicant claims SMALL ENTITY status. See 37 CFR 1.27.

❑ b. Applicant is no longer claiming SMALL ENTITY status. See 37 CFR 1.27(g)(2).

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

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

This collection of information is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
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 12/23/2011

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

EXAMINER	
SOROUSH, LAYLA	
ART UNIT	PAPER NUMBER
1627	

DATE MAILED: 12/23/2011

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)

(application filed on or after May 29, 2000)

The Patent Term Adjustment to date is 68 day(s). If the issue fee is paid on the date that is three months after the mailing date of this notice and the patent issues on the Tuesday before the date that is 28 weeks (six and a half months) after the mailing date of this notice, the Patent Term Adjustment will be 68 day(s).

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

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

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

Privacy Act Statement

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

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

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

Notice of Allowability	Application No.	Applicant(s)	
	10/525,006	SAWA ET AL.	
	Examiner	Art Unit	
	LAYLA SOROUSH	1627	

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

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

1. ☒ This communication is responsive to *the response to arguments submitted on September 6, 2011*.

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

3. ☒ The allowed claim(s) is/are *41,43-51,53-56,58-60 and 64-68*.

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

   a) ☒ All b) ☐ Some* c) ☐ None of the:

   1. ☒ Certified copies of the priority documents have been received.
   2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
   3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.

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

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

6. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.

   (a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review (PTO-948) attached

   1) ☐ hereto or 2) ☐ to Paper No./Mail Date _____.

   (b) ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

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

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

Attachment(s)

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

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

Authorization for this examiner's amendment was given in a telephone interview with Warren Cheek on December 16, 2011. This application has been amended as follows:

In claim 41, lines 3-4 after a hydrate thereof, **insert** – wherein the hydrate is at least one selected from a 1/2 hydrate, 1 hydrate, and 3/2 hydrate -- .

In claim 64, line 2-3 after a hydrate thereof, **insert** – wherein the hydrate is at least one selected from a 1/2 hydrate, 1 hydrate, and 3/2 hydrate -- .

Reasons for Allowance

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

The composition as claimed are found to be patentable over the prior art because the prior art does not teach or fairly suggest an aqueous liquid preparation consisting essentially of the following two components, wherein the first component is 2-amino-3-(4- bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof, and the second component is tyloxapol wherein said liquid preparation is formulated for ophthalmic administration, and wherein when a quaternary ammonium compound is included in said liquid preparation, the quaternary ammonium compound is benzalkonium chloride.

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

The closest prior arts of record, namely Yanni et al. and Desai et al. Yanni et al. teaches a composition comprising an active agent see specifically Preparation XV (3-benzoylphenylacetic acid derivatives, salts are known) in 0.01-0.5%, polysorbate 80 in 0.01%, benzalkonium chloride, disodium EDTA, monobasic sodium phosphate, dibasic sodium phosphate, sodium chloride, pH adjustment with NaOH and/or HCl, water. Desai et al. teach an ophthalmic composition comprising bromfenac (2-amino-3-(4-bromobenzoyl)phenylacetic acid) and its ophthalmically acceptable salts, esters, amides or prodrugs thereof (column 3, lines 13-29, claims 4 and 7) and polysorbates such as tweens and tyloxapol and further comprising boric acid buffer (column 2, lines 18-44).

Applicants have found that tyloxapol is not equivalent to polysorbate 80 when combined with bromfenac. The present inventors have discovered that tyloxapol has an unexpected property in stabilizing an aqueous solution ofbromfenac in comparison with polysorbate 80. Please see the description of Experimental Example 1 and Table 1 on pages 14-16 of the specification. In the Experimental Example, the stability of an aqueous solution ofbromfenac was measured by storing the bromfenac solution with polysorbate 80 (see Comparison Example 1) and, separately, with tyloxapol (see A-02), under conditions of pH 7.0 at 60℃ for 4 weeks. The remaining rate % of bromfenac was measured after the test. As shown in Table 1, only 51.3% ofbromfenac remained in the

aqueous solution when stored with polysorbate 80. In contrast, 73.8% of bromfenac remained in the aqueous solution when stored with tyloxapol. Thus the present inventors have found that tyloxapol has an unexpected stabilizing effect on an aqueous solution ofbromfenac in comparison to polysorbate 80. Therefore the present inventors have found that tyloxapol and polysorbate 80 are not equivalent compounds. Such unequivalency, and such remarkable effects, could not have been obvious to one skilled in the art from the cited references. For the foregoing reasons, it is respectfully submitted that the teachings of the cited references do not suggest the claimed bromfenac preparation as amended, nor the unexpected properties of the preparation. Additionally, Desai et al. teach that the problems with benzalkonium chloride and other quaternary ammonium compounds can be avoided by using certain polymeric quaternary ammonium compounds in combination with boric acid. Hence, an essential component of the Desai composition is a polymeric quaternary ammonium compound. However, the instant claims as amended require that, when the claimed liquid preparation includes a quaternary ammonium compound, the quaternary ammonium compound is limited to benzalkonium chloride. Thus the polymeric quaternary ammonium compounds disclosed in Desai et al. are excluded from the amended claims.

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

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

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

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

/SREENI PADMANABHAN/

Supervisory Patent Examiner, Art Unit 1627

Issue Classification	Application/Control No. 10/525,006	Applicant(s)/Patent under Reexamination SAWA ET AL.
	Examiner LAYLA SOROUSH	Art Unit 1627

ISSUE CLASSIFICATION

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

/Layla Soroush/ 12/5/11
(Assistant Examiner) (Date)

/Sreeni Padmanabhan/ 12/5/2011
(Legal Instruments Examiner) (Date)

(Primary Examiner) (Date)

Total Claims Allowed: 22

O.G. Print Claim(s)	O.G. Print Fig.
1	NONE

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

Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original
	1		31		61		91		121		151		181
	2		32		62		92		122		152		182
	3		33		63		93		123		153		183
	4		34	18	64		94		124		154		184
	5		35	19	65		95		125		155		185
	6		36	20	66		96		126		156		186
	7		37	21	67		97		127		157		187
	8		38	22	68		98		128		158		188
	9		39		69		99		129		159		189
	10		40		70		100		130		160		190
	11	1	41		71		101		131		161		191
	12		42		72		102		132		162		192
	13	2	43		73		103		133		163		193
	14	3	44		74		104		134		164		194
	15	4	45		75		105		135		165		195
	16	5	46		76		106		136		166		196
	17	6	47		77		107		137		167		197
	18	7	48		78		108		138		168		198
	19	8	49		79		109		139		169		199
	20	9	50		80		110		140		170		200
	21	10	51		81		111		141		171		201
	22		52		82		112		142		172		202
	23	11	53		83		113		143		173		203
	24	12	54		84		114		144		174		204
	25	13	55		85		115		145		175		205
	26	14	56		86		116		146		176		206
	27		57		87		117		147		177		207
	28	15	58		88		118		148		178		208
	29	16	59		89		119		149		179		209
	30	17	60		90		120		150		180		210

Search Notes	Application/Control No.	Applicant(s)/Patent under Reexamination	
	10/525,006	SAWA ET AL.	
	Examiner	Art Unit	
	LAYLA SOROUSH	1627	

SEARCHED			
Class	Subclass	Date	Examiner
514	619	12/5/11	LS
514	535	12/5/11	LS
514	570	12/5/11	LS

INTERFERENCE SEARCHED			
Class	Subclass	Date	Examiner
514	**618**	**12/5/11**	**LS**

SEARCH NOTES (INCLUDING SEARCH STRATEGY)		
	DATE	EXMR
STIC: npl and pat (4/28/11)	12/5/11	LS
odp	12/5/11	LS

UNITED STATES PATENT AND TRADEMARK OFFICE

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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 11/15/2011

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

EXAMINER	
SOROUSH, LAYLA	
ART UNIT	PAPER NUMBER
1627	

NOTIFICATION DATE	DELIVERY MODE
11/15/2011	ELECTRONIC

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

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

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

ddalecki@wenderoth.com
eoa@wenderoth.com

Applicant-Initiated Interview Summary	Application No.	Applicant(s)	
	10/525,006	SAWA ET AL.	
	Examiner	Art Unit	
	LAYLA SOROUSH	1627	

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

(1) *LAYLA SOROUSH*.

(2) *Sreeni Padmanabhan*.

(3) *Warren Cheek*.

(4)_____.

Date of Interview: *01 September 2011*.

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

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

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

Claim(s) discussed: *all claims of record*.

Identification of prior art discussed: *Yanni*.

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

Applicant argues - not necessarily is the claimed compound useful in the example
Applicant will consider amending claims to Bromfenac and tyloxapol
Applicant will deleter the method claims.

Applicant recordation instructions: 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

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

☐ Attachment

/Layla Soroush/ Examiner, Art Unit 1627	

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.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/525,006	03/28/2005	Shirou Sawa	2005_0232A	1756

513 7590 11/15/2011

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

EXAMINER	
SOROUSH, LAYLA	
ART UNIT	PAPER NUMBER
1627	

NOTIFICATION DATE	DELIVERY MODE
11/15/2011	ELECTRONIC

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

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

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

ddalecki@wenderoth.com
eoa@wenderoth.com

Office Action Summary	Application No.	Applicant(s)	
	10/525,006	SAWA ET AL.	
	Examiner	Art Unit	
	LAYLA SOROUSH	1627	

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

Period for Reply

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

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

Status

1)☒ Responsive to communication(s) filed on *06 September 2011*.

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

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

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

Disposition of Claims

5)☒ Claim(s) *41,43-51,53-56,58-60 and 64-68* is/are pending in the application.

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

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *41,43-51,53-56,58-60 and 64-68* is/are rejected.

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

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

Application Papers

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

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

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

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

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

Priority under 35 U.S.C. § 119

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

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

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

Attachment(s)

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

DETAILED ACTION

The response filed September 6, 2011 presents remarks and arguments submitted to the office action mailed May 6, 2011 is acknowledged.

Applicant's arguments over the 35 U.S.C. 103 (a) rejection of claims 41, 43-48, 50-51, 53-55, and 58-59 over as being unpatentable over Yanni et al. (5475034) in view of Guy et al.(5540930) is not persuasive. Therefore, the rejection of record is herewith maintained.

Applicant's arguments over the 35 U.S.C. 103 (a) rejection of claims 49, 56, 60, and 64-68 over as being unpatentable over P Yanni et al. (5475034) and Guy et al. (5540930), as applied to claims 41-48, 50-51, 53-55, and 58-59, and further in view of Gamache et al. (WO 01/15677) is not persuasive. Therefore, the rejection of record is herewith maintained.

The ODP rejection is maintained for the reasons of record.

The following rejections are made:

Claim Rejections - 35 USC § 103

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

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

Claims 41, 43-48, 50-51, 53-55, and 58-59 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yanni et al. (5475034) in view of Guy et al.(5540930).

Yanni et al. teaches a composition comprising an active agent see specifically Preparation XV (3-benzoylphenylacetic acid derivatives, salts are known) in 0.01-0.5%, polysorbate 80 in 0.01%, benzalkonium chloride, disodium EDTA, monobasic sodium phosphate, dibasic sodium phosphate, sodium chloride, pH adjustment with NaOH and/or HCl, water.

The reference fails to teach the specific elected second agent tyloxapol.

Guy et al. teaches non-ionic surfactant surface active agent include polysorbate 80 and tyloxapol in 0.05-1%.

It would have been obvious to one of ordinary skill in the art at the time of the invention to interchange polysorbate 80 and tyloxapol. The motivation comes from the teaching of Guy et al. that both compounds are non-ionic surfactant surface active agents. Hence, a skilled artisan would have had reasonable expectation of successfully producing a composition with similar efficacy and results.

Claims 49, 56, 60, and 64-68 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yanni et al. (5475034) and Guy et al. (5540930), as applied to claims 41-48, 50-51, 53-55, and 58-59, and further in view of Gamache et al. (WO 01/15677).

Yanni et al. and Guy et al. are as applied above.

Yanni et al. and Guy et al. do not teach the specific buffer boric acid and/or sodium borate/sodium tetraborate; thickners, polyvinylpyrrolidone; stabilizer is sodium sulfite.

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

It would have been obvious to one of ordinary skill in the art at the time of the invention to use the specific buffer boric acid and/or sodium borate/sodium tetraborate; thickners, polyvinylpyrrolidone; stabilizer is sodium sulfite. The motivation comes from the teaching of Gamache et al. that the anti-inflammatory agents, viscosity building agents, and buffer systems are interchangeable. Hence, a skilled artisan would have had reasonable expectation of successfully producing a composition with similar efficacy and results.

Double Patenting

Claims 41-51, 53-56, 58-60 and 64-68 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's main argument is that "Bromfenac is mentioned in Yanni in Table 1, merely as a reference compound for comparison purposes with the novel amide and ester derivatives of Yanni. It can be seen from the description of the anti-inflammatory tests described in columns 13 and 14 that bromfenac was tested merely in a 0.1% solution of the compound, and not in a pharmaceutical composition." Examiner states Yanni clearly discloses a single topical dose of 0.1% drug solution/suspension comprising Bromfenac. The Examiners

contention is that the reference does not specify the specific components of the comparative formulation (or in fact, the novel formulations) of the tests. However, the Example of the ophthalmic composition disclosing 0.01-0.5% of an active agent in a formulation renders obvious the use of the comparative example- Bromfenac, in such a formulation.

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

Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

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

Conclusion

No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Layla Soroush whose telephone number is

(571)272-5008. The examiner can normally be reached on Monday through Friday from 8:30 a.m. to 5:00 p.m.

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

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/SREENI PADMANABHAN/

Supervisory Patent Examiner, Art Unit 1627

Search Notes	Application/Control No.	Applicant(s)/Patent under Reexamination	
	10/525,006	SAWA ET AL.	
	Examiner	Art Unit	
	LAYLA SOROUSH	1627	

SEARCHED			
Class	Subclass	Date	Examiner

INTERFERENCE SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES (INCLUDING SEARCH STRATEGY)		
	DATE	EXMR
tyloxapol and bromfenac	11/7/11	LS
odp	11/7/11	LS

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 1627
Filed March 28, 2005	:	Examiner Layla Soroush
AQUEOUS LIQUID PREPARATION CONTAINING 2-AMINO-3-(4-BROMOBENZOYL)PHENYLACETIC ACID	:	**Mail Stop: Amendment**

AMENDMENT

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

Sir:

Responsive to the Official Action dated May 6, 2011, the time for responding thereto being extended for one month in accordance with a petition for extension submitted concurrently herewith, please amend the above-identified application as follows:

REMARKS

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

Applicants wish to thank the Examiner Soroush and SPE Padmanabhan for their courtesy and assistance provided to the Applicants' representative during the personal interview held on September 1, 2011.

The claims have been amended as proposed by the Applicants and as suggested by the Examiners. Specifically, the second component has been limited to tyloxapol to expedite allowance. Such limitation is made without prejudice to the filing of a divisional application. Claim 41 has been amended to remove the "limited to" phrase, and method claims 61-62 are cancelled without prejudice.

Turning to the rejections, claims 41-48, 50-51, 53-55 and 58-59 are rejected under 35 USC 103 as unpatentable over Yanni in view of Guy. Such rejection is respectfully traversed as applied to the amended claims.

As discussed during the interview, the rejection appears to take the position that Yanni discloses in Preparation XV a composition of bromfenac with polysorbate 80. However Preparation XV does not disclose bromfenac, the acid, but an amide derivative thereof.

Moreover, Yanni teaches that bromfenac acids have problems such as difficulty in formulating stable solutions, and provoking ocular irritation. See column 1, line 60 to column 2, line 3. The object of Yanni is to make amide and ester derivatives of bromfenac which the inventors found to have better stability while having similar anti-inflammatory activity. See for example column 2, lines 23-43.

Bromfenac is mentioned in Yanni in Table 1, merely as a reference compound for comparison purposes with the novel amide and ester derivatives of Yanni. It can be seen from the description of the anti-inflammatory tests described in columns 13 and 14 that bromfenac was tested merely in a 0.1% solution of the compound, and not in a pharmaceutical composition.

The pharmaceutical compositions disclosed in the Tables of columns 16 and 17 of Yanni are directed to compositions of an "Active Agent" with polysorbate 80 and other components. The "Active Agent" is defined on lines 50-51 of column 16 to mean "one or more compounds of Formula I". The compounds of Formula I are described from the bottom of column 2 to 3. From

the definition of "Y" in the compounds, it is apparent that these compounds are limited to the amide or ester of bromfenac and do not encompass the bromfenac acid itself.

In summary, neither Preparation XV nor the remainder of Yanni disclose a composition of bromfenac as claimed, or its salt or hydrate, together with polysorbate 80 as contended in the rejection.

Moreover, Yanni teach away from using bromfenac as claimed, due to problems with obtaining stable solutions and provoking ocular irritation. See column 1 line 60 to column 2 line 3.

Therefore Yanni do not teach or suggest a composition of bromfenac with polysorbate 80.

Guy is cited for teaching the equivalency of polysorbate 80 and tyloxapol.

However Guy is directed to solving the problem of agglomeration of water insoluble steroid compounds such as loteprednol etabonate. See for example column 2, lines 45-65. On the other hand, bromfenac is a nonsteroidal compound.

Therefore one skilled in the art would not have been motivated to combine the teachings of Yanni directed to nonsteroidal compositions with Guy directed to steroidal compositions.

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).

Moreover, the present inventors have found that tyloxapol is not equivalent to polysorbate 80 when combined with bromfenac.

The present inventors have discovered that tyloxapol has an unexpected property in stabilizing an aqueous solution of bromfenac in comparison with polysorbate 80. Please see the description of Experimental Example 1 and Table 1 on pages 14-16 of the specification.

In the Experimental Example, the stability of an aqueous solution of bromfenac was measured by storing the bromfenac solution with polysorbate 80 (see Comparison Example 1) and, separately, with tyloxapol (see A-02), under conditions of pH 7.0 at 60°C for 4 weeks. The remaining rate % of bromfenac was measured after the test.

As shown in Table 1, only 51.3% of bromfenac remained in the aqueous solution when stored with polysorbate 80. In contrast, 73.8% of bromfenac remained in the aqueous solution when stored with tyloxapol.

Thus the present inventors have found that tyloxapol has an unexpected stabilizing effect on an aqueous solution of bromfenac in comparison to polysorbate 80. Therefore the present inventors have found that tyloxapol and polysorbate 80 are not equivalent compounds. Such unequivalency, and such remarkable effects, could not have been obvious to one skilled in the art from the cited references.

For the foregoing reasons, it is respectfully submitted that the teachings of the cited references do not suggest the claimed bromfenac preparation as amended, nor the unexpected properties of the preparation.

Claims 49, 56, 60 and 64-68 are rejected under 103 as unpatentable over Yanni, Guy and Gamache.

The rejection of these claims is believed to be overcome in view of the foregoing amendments and remarks.

Lastly, claims 41-51, 53-56, 58-60 and 64-68 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.

It is believed that all other grounds of rejection have been overcome in view of the instant response. Accordingly, 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.

/Warren M. Cheek/

Digitally signed by /Warren M. Cheek/
DN: cn=/Warren M. Cheek/, o, ou, email=wcheek@wenderoth.com, c=US
Date: 2011.09.06 13:39:04 -04'00'

By _____

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

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September 6, 2011

Electronic Patent Application Fee Transmittal

Application Number:	10525006
Filing Date:	28-Mar-2005
Title of Invention:	Aqueous liquid preparation containing 2-amino-3-(4-bromobenzoyl) phenylacetic acid
First Named Inventor/Applicant Name:	Shirou Sawa
Filer:	Warren M. Cheek Jr./Donna King
Attorney Docket Number:	2005_0232A

Filed as Large Entity

U.S. National Stage under 35 USC 371 Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Extension - 1 month with $0 paid	1251	1	130	130

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
			Total in USD ($)	**130**

Electronic Acknowledgement Receipt

EFS ID:	10881730
Application Number:	10525006
International Application Number:	
Confirmation Number:	1756
Title of Invention:	Aqueous liquid preparation containing 2-amino-3-(4-bromobenzoyl) phenylacetic acid
First Named Inventor/Applicant Name:	Shirou Sawa
Customer Number:	00513
Filer:	Warren M. Cheek Jr./sarah pedersen
Filer Authorized By:	Warren M. Cheek Jr.
Attorney Docket Number:	2005_0232A
Receipt Date:	06-SEP-2011
Filing Date:	28-MAR-2005
Time Stamp:	14:46:53
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	yes
Payment Type	Credit Card
Payment was successfully received in RAM	$130
RAM confirmation Number	1111
Deposit Account	230975
Authorized User	CHEEK JR.,WARREN M.

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

Charge any Additional Fees required under 37 C.F.R. 1.492 (National application filing, search, and examination fees)

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

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

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

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

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		AttachA_Pa.pdf	287499 b096e5aa7dc2a34dd83fc2b2095cdfb82761c9d9	yes	9

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Preliminary Amendment	1	1
	Claims	2	5
	Applicant Arguments/Remarks Made in an Amendment	6	9

Warnings:

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

Information:

2	Fee Worksheet (SB06)	fee-info.pdf	30367 41ca859b0adda093107ca323e4824f411c3449fe	no	2

Warnings:

Information:

Total Files Size (in bytes):	317866

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

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

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

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

PTO/SB/06 (07-06)
Approved for use through 1/31/2007. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number	Filing Date	☐ To be Mailed
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))							
			TOTAL			TOTAL	

* If the difference in column 1 is less than zero, enter "0" in column 2.

APPLICATION AS AMENDED – PART II

AMENDMENT	09/06/2011	(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))	* 22	Minus	** 45	= 0	X $ =		OR	X $52=	0
	Independent (37 CFR 1.16(h))	* 2	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:
/DIANA BATES/

Amendments to the Claims

1-40. (Cancelled)

41. (Currently amended) An aqueous liquid preparation consisting essentially of the following two components, wherein the first component is 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof, and the second component is tyloxapol ~~an alkyl-aryl-polyether alcohol type polymer or a polyethylene glycol fatty acid ester~~, wherein said liquid preparation is formulated for ophthalmic administration, and wherein when a quaternary ammonium compound is included in said liquid preparation, the quaternary ammonium compound is ~~limited to~~ benzalkonium chloride.

42. (Cancelled)

43. (Previously presented) The aqueous liquid preparation according to claim 41, wherein the first component is a 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt.

44. (Previously presented) The aqueous liquid preparation according to claim 41, wherein the second component is tyloxapol and the pharmacologically acceptable salt of 2-amino-3-(4-bromobenzoyl)phenylacetic acid is a sodium salt , wherein the concentration of the tyloxapol is from about 0.01 w/v % to about 0.5 w/v %; and

wherein the first component is a 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt, wherein the concentration of the 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt is from about 0.01 to about 0.5 w/v %.

45. (Previously presented) The aqueous liquid preparation according to claim 44, wherein the concentration of the tyloxapol is from about 0.01 w/v % to about 0.3 w/v % and the concentration of the 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt is from about 0.05 to about 0.2 w/v %.

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 45, wherein the concentration of the tyloxapol is about 0.02 w/v %.

48. (Previously presented) The aqueous liquid preparation according to claim 41, 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 49, 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 45, 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.

61-63. (Cancelled)

64. (Previously presented) An aqueous liquid preparation consisting essentially of:
(a) 2-amino-3-(4- bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof,
(b) tyloxapol,
(c) boric acid,
(d) sodium tetraborate,
(e) EDTA sodium salt,
(f) benzalkonium chloride,
(g) polyvinylpyrrolidone, and
(h) sodium sulfite, ~~and~~
wherein said liquid preparation is formulated for ophthalmic administration, and
wherein benzalkonium chloride is the only quaternary ammonium compound which is included in said liquid preparation.

65. (Previously presented) The aqueous liquid preparation of claim 64, wherein (a) is a 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt.

66. (Previously presented) The aqueous liquid preparation of claim 65, wherein the concentration of the 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt is from about 0.01 to about 0.5 w/v % and the concentration of the tyloxapol is about 0.02 w/v %.

67. (Previously presented) The aqueous liquid preparation of claim 66, wherein the concentration of the 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt is about 0.01 w/v %.

68. (Previously presented) The aqueous liquid preparation of claim 66, wherein the concentration of the 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt is about 0.1 w/v %.

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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 05/06/2011

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

EXAMINER	
SOROUSH, LAYLA	

ART UNIT	PAPER NUMBER
1627	

NOTIFICATION DATE	DELIVERY MODE
05/06/2011	ELECTRONIC

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

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

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

ddalecki@wenderoth.com
eoa@wenderoth.com

Office Action Summary	Application No.	Applicant(s)	
	10/525,006	SAWA ET AL.	
	Examiner	Art Unit	
	LAYLA SOROUSH	1627	

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

Period for Reply

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

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

Status

1)☒ Responsive to communication(s) filed on *25 October 2010*.

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) *41-51,53-56,58-62 and 64-68* is/are pending in the application.

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

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *41-51,53-56,58-60 and 64-68* 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 _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on October 25, 2010 has been entered.

The original restriction election is carried over from the response to the office action mailed on July 24, 2007.

The following rejections are made:

Claim Rejections - 35 USC § 103

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

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

Claims 41-48, 50-51, 53-55, and 58-59 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yanni et al. (5475034) in view of Guy et al.(5540930).

Yanni et al. teaches a composition comprising an active agent see specifically Preparation XV (3-benzoylphenylacetic acid derivatives, salts are known) in 0.01-0.5%, polysorbate 80 in 0.01%, benzalkonium chloride, disodium EDTA, monobasic sodium

phosphate, dibasic sodium phosphate, sodium chloride, pH adjustment with NaOH and/or HCl, water.

The reference fails to teach the specific elected second agent tyloxapol.

Guy et al. teaches non-ionic surfactant surface active agent include polysorbate 80 and tyloxapol in 0.05-1%.

It would have been obvious to one of ordinary skill in the art at the time of the invention to interchange polysorbate 80 and tyloxapol. The motivation comes from the teaching of Guy et al. that both compounds are non-ionic surfactant surface active agents. Hence, a skilled artisan would have had reasonable expectation of successfully producing a composition with similar efficacy and results.

Claims 49, 56, 60, and 64-68 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yanni et al. (5475034) and Guy et al. (5540930), as applied to claims 41-48, 50-51, 53-55, and 58-59, and further in view of Gamache et al. (WO 01/15677).

Yanni et al. and Guy et al. are as applied above.

Yanni et al. and Guy et al. do not teach the specific buffer boric acid and/or sodium borate/sodium tetraborate; thickners, polyvinylpyrrolidone; stabilizer is sodium sulfite.

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

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

It would have been obvious to one of ordinary skill in the art at the time of the invention to use the specific buffer boric acid and/or sodium borate/sodium tetraborate; thickners, polyvinylpyrrolidone; stabilizer is sodium sulfite. The motivation comes from the teaching of Gamache et al. that the anti-inflammatory agents, viscosity building agents, and buffer systems are interchangeable. Hence, a skilled artisan would have had reasonable expectation of successfully producing a composition with similar efficacy and results.

Double Patenting

Claims 41-51, 53-56, 58-60 and 64-68 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's arguments filed October 25, 2010 have been fully considered. The response to the arguments is as discussed below:

Applicant's arguments with respect to claims 41-51, 53-56, and 58-60, and 64-68 have been considered but are moot in view of the new ground(s) of rejection. More specifically, the Applicant states the Polyquad component is required in the Desai et al. reference while the amended claims herein are drawn to a composition wherein when a quaternary ammonium compound is included in said liquid preparation, the quaternary ammonium compound is limited to benzalkonium chloride. The newly modified rejections above address the amendments made to the claims.

Conclusion

No claims allowed.

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

5008. The examiner can normally be reached on Monday through Friday from 8:30 a.m. to 5:00 p.m.

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

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/SREENI PADMANABHAN/

Supervisory Patent Examiner, Art Unit 1627

Notice of References Cited	Application/Control No. 10/525,006	Applicant(s)/Patent Under Reexamination SAWA ET AL.	
	Examiner LAYLA SOROUSH	Art Unit 1627	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
*	A	US-5,475,034	12-1995	Yanni et al.	514/619
*	B	US-5,540,930	07-1996	Guy et al.	424/427
	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	WO 0115677 A2	03-2001	World Intellect	GAMACHE D A et al.	
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

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

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

(19) World Intellectual Property Organization
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(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-Hydroxytryptamine1Dß Receptor*, Molecular Pharmacology, volume 41, pages 1-7 (1992) and Hoyer et al., *VII. International Union of Pharmacology Classification of Receptors for 5-Hydroxytryptamine (Serotonin)*, Pharmacological Reviews, volume 46, no. 2, pages 157-170 (1994)).

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

Summary of the Invention

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

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

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

Detailed Description of the Invention

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Example 1

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

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

Example 2

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

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

Example 3

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

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

Example 4

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

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

What is claimed is:

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Search Notes	Application/Control No.	Applicant(s)/Patent under Reexamination	
	10/525,006	SAWA ET AL.	
	Examiner	Art Unit	
	LAYLA SOROUSH	1627	

SEARCHED			
Class	Subclass	Date	Examiner

INTERFERENCE SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES (INCLUDING SEARCH STRATEGY)		
	DATE	EXMR
STIC: npl; pat; odp	4/28/2011	LS

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 01/20/2011

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
1619	

NOTIFICATION DATE	DELIVERY MODE
01/20/2011	ELECTRONIC

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

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

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

ddalecki@wenderoth.com
eoa@wenderoth.com

Interview Summary	Application No.	Applicant(s)	
	10/525,006	SAWA ET AL.	
	Examiner	Art Unit	
	Donna Jagoe	1619	

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

(1) *Donna Jagoe*. (3)_____.

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

Date of Interview: *14 January 2011*.

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: *The claims in general*.

Identification of prior art discussed: *Desai et al. of record*.

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: *See Continuation Sheet*.

(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.

/Donna Jagoe/ Examiner, Art Unit 1619	/Robert A. Wax/ Supervisory Patent Examiner, Art Unit 1615

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 Substance of Interview including description of the general nature of what was agreed to if an agreement was reached, or any other comments: Applicants' representative pointed out changes to the independent claims to limit the quaternary ammonium compound to benzalkonium chloride. This amendment would specifically exclude polymeric quaternary ammonium compounds, necessary for the composition of Desai et al. Desai et al. teaches away from benzalkonium chloride with ophthamic compositions of drugs with acidic groups such as NSAIDs because they lose their ability to function because they form complexes with the charged drug compounds (column 1, lines 27-34)..

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REQUEST for CONTINUED EXAMINATION (RCE) TRANSMITTAL

Address to:
Mail Stop RCE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Application Number	10/525,006
Filing Date	March 28, 2005
First Named Inventor	Shirou SAWA et al.
Group Art Unit	1614
Examiner Name	Donna A. Jagoe
Attorney Docket Number	2005_0232A
Confirmation No.	1756

This is a Request for Continued Examination (RCE) under 37 C.F.R. § 1.114 of the above-identified application.
Request for Continued Examination (RCE) practice under 37 CFR 1.114 does not apply to any utility or plant application filed prior to June 8, 1995, or to any design application. See Instruction Sheet for RCEs (not to be submitted to the USPTO) on page 2.

1. **Submission required under 37 C.F.R. § 1.114 -- Note: If the RCE is proper, any previously filed unentered amendments and amendments enclosed with the RCE will be entered in the order in which they were filed unless applicant instructs otherwise. If applicant does not wish to have any previously filed unentered amendment(s) entered, applicant must request non-entry of such amendment(s).**
   a. [ ] Previously submitted. If a final Office Action is outstanding, any amendments filed after the final Office Action may be considered as a submission even if this box is not checked.
      I. [ ] Please consider the arguments in the Appeal Brief or Reply Brief previously filed on
      II. [ ] Other

   b. [X] Enclosed:
      I. [X] Amendment/Reply
      II. [ ] Affidavit(s)/Declaration(s)
      III. [ ] Information Disclosure Statement (IDS)
      IV. [X] Other: - **Request for Personal Interview**

2. **Miscellaneous**
   a. [ ] Suspension of action on the above-identified application is required under 37 C.F.R. § 1.103(c) for a period of months (period of suspension shall not exceed 3 months; Fee under 37 C.F.R. § 1.17(i) required).

   b. [ ] Other

3. **Fees (The RCE fee under 37 C.F.R. § 1.17(e) is required by 37 C.F.R. § 1.114 when the RCE is filed.)**
   a. [] The Director is hereby authorized to charge the following fees to Deposit Account No. 23-0975.
      I. [ ] RCE fee required under 37 C.F.R. § 1.17(e)
      II. [ ] Extension of time fee (37 C.F.R. § 1.136 and § 1.17)
      III. [] Other:

   b. [] Check in the amount of $ enclosed

   c. [X] Payment is made by Credit Card for the following fees (Credit Card Payment Form Enclosed) in the amount of $810.00:
      I. [X] RCE fee required under 37 C.F.R. § 1.17(e)
      II. [X] Extension of time fee (37 C.F.R. § 1.136 and § 1.17)
      III. [ ] Other:

4. CORRESPONDENCE ADDRESS

CUSTOMER NO.
000513

/Warren M. Cheek/
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Date: 2010.10.25 14:57:03 -04'00'

By: Warren M. Cheek
Registration No. 33,367

WENDEROTH, LIND & PONACK, L.L.P.
1030 15th Street, N.W., Suite 400 East
Washington, D.C. 20005-1503
Phone:(202) 721-8200
Fax:(202) 721-8250

October 25, 2010

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

Electronic Patent Application Fee Transmittal

Application Number:	10525006
Filing Date:	28-Mar-2005
Title of Invention:	Aqueous liquid preparation containing 2-amino-3-(4-bromobenzoyl) phenylacetic acid
First Named Inventor/Applicant Name:	Shirou Sawa
Filer:	Warren M. Cheek Jr./Donna King
Attorney Docket Number:	2005_0232A

Filed as Large Entity

U.S. National Stage under 35 USC 371 Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Extension - 1 month with $0 paid	1251	1	130	130

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
Request for continued examination	1801	1	810	810
		Total in USD ($)		**940**

Electronic Acknowledgement Receipt

EFS ID:	8694091
Application Number:	10525006
International Application Number:	
Confirmation Number:	1756
Title of Invention:	Aqueous liquid preparation containing 2-amino-3-(4-bromobenzoyl) phenylacetic acid
First Named Inventor/Applicant Name:	Shirou Sawa
Customer Number:	00513
Filer:	Warren M. Cheek Jr./sarah pedersen
Filer Authorized By:	Warren M. Cheek Jr.
Attorney Docket Number:	2005_0232A
Receipt Date:	25-OCT-2010
Filing Date:	28-MAR-2005
Time Stamp:	15:41:33
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	yes
Payment Type	Credit Card
Payment was successfully received in RAM	$940
RAM confirmation Number	2296
Deposit Account	230975
Authorized User	CHEEK JR.,WARREN M.

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

Charge any Additional Fees required under 37 C.F.R. 1.492 (National application filing, search, and examination fees)

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

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

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

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

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Extension of Time	AttachA_Eot.pdf	187187 d76c294124cd1d515c57d32add5dd1b69d00e6c8	no	1
Warnings:					
The PDF file has been signed with a digital signature and the legal effect of the document will be based on the contents of the file not the digital signature.					
Information:					
2	Miscellaneous Incoming Letter	AttachC_Int.pdf	189989 fff03f165d72817e574814a199c83db92d74297b	no	1
Warnings:					
The PDF file has been signed with a digital signature and the legal effect of the document will be based on the contents of the file not the digital signature.					
Information:					
3	Amendment Submitted/Entered with Filing of CPA/RCE	AttachD_Pa.pdf	305460 3126cc9f781eeccd386a0e53cbdd1ba2e394656c	no	11
Warnings:					
The PDF file has been signed with a digital signature and the legal effect of the document will be based on the contents of the file not the digital signature.					
Information:					
4	Request for Continued Examination (RCE)	AttachB_Rce.pdf	63032 8efcd85268663d7c5864119367b813b4cf691ec7	no	1
Warnings:					
This is not a USPTO supplied RCE SB30 form.					
Information:					
5	Fee Worksheet (PTO-875)	fee-info.pdf	32313 2754ab60d2a4eab72d1ed19474d4fb599d38784e	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	777981		

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

New Applications Under 35 U.S.C. 111

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

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

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

New International Application Filed with the USPTO as a Receiving Office

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

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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 24, 2010.

The fee of $130.00 is charged to Credit Card.

Respectfully submitted,

Shirou SAWA et al.

By /Warren M. Cheek/

Digitally signed by /Warren M. Cheek/
DN: cn=/Warren M. Cheek/, o, ou, email=wcheek@wenderoth.com, c=US
Date: 2010.10.25 14:56:42 -04'00'

Warren M. Cheek
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Attorney for Applicants

WMC/dlk
Washington, D.C. 20005-1503
Telephone (202) 721-8200
Facsimile (202) 721-8250
October 25, 2010

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

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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**

REQUEST FOR PERSONAL INTERVIEW

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

Sir:

A personal interview is request with the Examiner prior to issuance of the first Office Action in this RCE.

Respectfully submitted,

Shirou SAWA et al.

By /Warren M. Cheek/

Digitally signed by /Warren M. Cheek/
DN: cn=/Warren M. Cheek/, o, ou, email=wcheek@wenderoth.com, c=US
Date: 2010.10.25 14:57:21 -04'00'

Warren M. Cheek
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Facsimile (202) 721-8250
October 25, 2010

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

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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**

PRELIMINARY AMENDMENT

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

Sir:

The present Amendment is filed concurrently with an RCE, and is responsive to the Official Action dated June 24, 2010.

Please amend the above-identified application as follows:

Amendments to the Claims

1-40. (Cancelled)

41. (Currently amended) An aqueous liquid preparation consisting essentially of the following two components, wherein the first component is 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof, and the second component is an alkyl aryl polyether alcohol type polymer or a polyethylene glycol fatty acid ester, wherein said liquid preparation is formulated for ophthalmic administration, and wherein when a quaternary ammonium compound is included in said liquid preparation, the quaternary ammonium compound is limited to benzalkonium chloride.

42. (Previously presented) The aqueous liquid preparation according to claim 41, wherein the second component is tyloxapol.

43. (Previously presented) The aqueous liquid preparation according to claim 41, wherein the first component is a 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt.

44. (Previously presented) The aqueous liquid preparation according to claim 41, wherein the second component is tyloxapol and the pharmacologically acceptable salt of 2-amino-3-(4-bromobenzoyl)phenylacetic acid is a sodium salt , wherein the concentration of the tyloxapol is from about 0.01 w/v % to about 0.5 w/v %; and

wherein the first component is a 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt, wherein the concentration of the 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt is from about 0.01 to about 0.5 w/v %.

45. (Previously presented) The aqueous liquid preparation according to claim 44, wherein the concentration of the tyloxapol is from about 0.01 w/v % to about 0.3 w/v % and the concentration of the 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt is from about 0.05 to about 0.2 w/v %.

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 45, wherein the concentration of the tyloxapol is about 0.02 w/v %.

48. (Previously presented) The aqueous liquid preparation according to claim 41, 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 49, 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 45, 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 the following two components, the first component being 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof, and the second component being tyloxapol or polyethylene glycol monostearate, wherein said liquid preparation is formulated for ophthalmic administration, and wherein when a quaternary ammonium compound is included in said liquid preparation, the quaternary ammonium compound is limited to benzalkonium chloride.

62. (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 consisting essentially of the following two components, the first component being 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof, and the second component being tyloxapol or polyethylene glycol monostearate, together with a preservative, wherein said liquid preparation is formulated for ophthalmic administration, and wherein when a quaternary ammonium compound is included in said liquid preparation, the quaternary ammonium compound is limited to benzalkonium chloride.

63. (Cancelled)

64. (Currently amended) An aqueous liquid preparation consisting essentially of:
(a) 2-amino-3-(4- bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof,
(b) tyloxapol,

(c) boric acid,

(d) sodium tetraborate,

(e) EDTA sodium salt,

(f) benzalkonium chloride,

(g) polyvinylpyrrolidone, and

(h) sodium sulfite, ~~and~~

wherein said liquid preparation is formulated for ophthalmic administration, and

wherein benzalkonium chloride is the only quaternary ammonium compound which is included in said liquid preparation.

65. (Previously presented) The aqueous liquid preparation of claim 64, wherein (a) is a 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt.

66. (Previously presented) The aqueous liquid preparation of claim 65, wherein the concentration of the 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt is from about 0.01 to about 0.5 w/v % and the concentration of the tyloxapol is about 0.02 w/v %.

67. (Previously presented) The aqueous liquid preparation of claim 66, wherein the concentration of the 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt is about 0.01 w/v %.

68. (Previously presented) The aqueous liquid preparation of claim 66, wherein the concentration of the 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt is about 0.1 w/v %.

REMARKS

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

A personal interview with the Examiner is respectfully requested prior to issuance of a first Office Action in this RCE application.

Claims 41, 61 and 62 have been amended to require that "when a quaternary ammonium compound is included in said liquid preparation, the quaternary ammonium compound is limited to benzalkonium chloride". Support for this limitation is found, for example, in the paragraph bridging pages 3-4 of the specification; and on lines 3-7 on page 12 of the specification. Claim 64, which requires benzalkonium chloride, has similarly been amended to require that "benzalkonium chloride is the only quaternary ammonium compound which is included in said liquid preparation".

Turning to the last Official Action, claims 41-42 are newly rejected as anticipated under 35 U.S.C. 102 by U.S. Patent No. 5,603,929 to Desai et al. This ground of rejection is deemed to be untenable as applied to the claims after the foregoing amendments for the following reasons.

Desai et al. teach at column 1, lines 27-34 that:

> Benzalkonium chloride is a widely used preservative in ophthalmic solutions. However, benzalkonium chloride and other quaternary ammonium compounds are generally considered to be incompatible with ophthalmic compositions of drugs with acidic groups, such as nonsteroidal anti-inflammatory drugs ("NSAIDS"). These preservative [sic] lose their ability to function as they form complexes with the charged drug compounds.

As recognized by the Examiner, bromfenac used in the claimed preparation is an acidic "NSAID" drug.

Desai et al. further note at column 2, lines 1-5 that:

> The use of POLYQUAD® and other polymeric quaternary ammonium compounds as a disinfectant and preservative in

> contact lens care and artificial tear solutions is known. See, for example, U.S. Pat. Nos. 5,037,647; 4,525,346; and 4,407,791.

Desai et al. summarize the intended purpose of their invention at column 2, lines 18-30 as follows:

> It has now been discovered that the use of a combination of a polymeric quaternary ammonium compound such as POLYQUAD® and boric acid in ophthalmic compositions of acidic drugs provides a storage-stable composition which has surprisingly good preservative efficacy. This preservative combination of a polymeric quaternary ammonium compound and boric acid is useful in ophthalmic compositions of acidic drugs such as prostaglandins, antifungals, antibactedals [sic], and diagnostic agents. This preservative combination is especially useful in ophthalmic solutions of drugs containing either a carboxyl group such as non-steroidal anti-inflammatory drugs (NSAIDS) or a sulfonamide group such as antibacterial drugs.

Desai et al. further mention at column 3, lines 30-38 that:

> The compositions of the present invention may additionally include other ophthalmically acceptable components such as …. other preservatives (e.g. benzalkonium chloride) … tyloxapol…

Thus, Desai et al. teach away from using a quaternary ammonium compound such as benzalkonium chloride as a preservative with acidic NSAID drugs like bromfenac. Desai et al. teach that the problems with benzalkonium chloride and other quaternary ammonium compounds can be avoided by using certain polymeric quaternary ammonium compounds in combination with boric acid.

Hence, an essential component of the Desai composition is a polymeric quaternary ammonium compound.

However, the instant claims as amended require that, when the claimed liquid preparation includes a quaternary ammonium compound, the quaternary ammonium compound is limited to benzalkonium chloride.

Thus the polymeric quaternary ammonium compounds disclosed in Desai et al. are excluded from the amended claims.

Therefore the amended claims 41-42 are not anticipated by Desai et al.

Claims 43-51, 53-56, 58-60 and 64-68 are newly rejected as obvious under 35 U.S.C. 103 over Desai et al. in view of U.S. Patent No. 5,475,034 to Yanni et al. and U.S. Patent No. 5,998,465 to Hellberg et al. This ground of rejection is deemed to be untenable as applied to the claims after the foregoing amendments for the following reasons.

As discussed above, each independent claim 41, 61 and 62 has been amended to require that "when a quaternary ammonium compound is included in said liquid preparation, the quaternary ammonium compound is limited to benzalkonium chloride". In addition, independent claim 64, which requires benzalkonium chloride, has similarly been amended to require that "benzalkonium chloride is the only quaternary ammonium compound which is included in said liquid preparation".

Thus, the instant claims as amended require that, when the claimed liquid preparation includes a quaternary ammonium compound, the quaternary ammonium compound is limited to benzalkonium chloride.

On the other hand, Desai et al. teach away from using a quaternary ammonium compound such as benzalkonium chloride as a preservative with acidic NSAID drugs like bromfenac. Desai et al. teach that the problems with benzalkonium chloride and other quaternary ammonium compounds can be avoided by using certain polymeric quaternary ammonium compounds in combination with boric acid.

Hence, an essential component of the Desai composition is a polymeric quaternary ammonium compound. However the polymeric quaternary ammonium compounds disclosed in Desai et al. are excluded from the amended claims.

There is no motivation or suggestion in the cited prior art to modify the Desai composition to replace the polymeric quaternary ammonium compound taught in Desai et al. with benzalkonium chloride. The intended purpose of the invention disclosed in Desai et al., as mentioned above, is to provide a storage-stable ophthalmic composition for acidic NSAID drugs,

like bromfenac, having good preservative efficacy. This preservative combination is a polymeric quaternary ammonium compound and boric acid.

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, a substitution of the Desai polymeric quaternary ammonium compound with benzalkonium chloride would render the Desai et al. invention unsatisfactory for its intended purpose.

Applicant therefore respectfully submits a prima facie case of obviousness cannot be based on the combination of Desai et al. with Yanni et al. and Hellberg et al.

In addition to the argument that the proposed modification changes the principle operation and intended purpose of Desai et al., Applicant reiterates that Desai et al. explicitly teach away from the use of a quaternary ammonium compound, such as benzalkonium chloride, as the only quaternary ammonium compound in an ophthalmic solution for an acidic NSAID drug such as bromfenac.

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).

For the reasons detailed above, Applicant respectfully requests withdrawal of the rejection of all claims under 35 USC 103 as being unpatentable over Desai et al., Yanni et al. and Hellberg et al.

Lastly, claims 41-51, 53-56, 58-60 and 64-68 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.

It is believed that all other grounds of rejection have been overcome in view of the instant response. Accordingly, 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.

Rejoinder and allowance of the withdrawn method claims is also solicited.

Respectfully submitted,

Shirou SAWA et al.

/Warren M. Cheek/

Digitally signed by /Warren M. Cheek/
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Date: 2010.10.25 14:57:48 -04'00'

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October 25, 2010

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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	10/25/2010	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE ($)	SMALL ENTITY ADDITIONAL FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 25	Minus	** 45	= 0	X $ =		OR	X $52=	0
	Independent (37 CFR 1.16(h))	* 4	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 ($)	ADDITIONAL FEE ($)	OR	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:
/JAMILAH Z. HARRIS/

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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 06/24/2010

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EXAMINER	
JAGOE, DONNA A	

ART UNIT	PAPER NUMBER
1619	

NOTIFICATION DATE	DELIVERY MODE
06/24/2010	ELECTRONIC

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

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

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

ddalecki@wenderoth.com
eoa@wenderoth.com

Office Action Summary	Application No.	Applicant(s)	
	10/525,006	SAWA ET AL.	
	Examiner	Art Unit	
	Donna Jagoe	1619	

-- 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 *24 March 2010*.

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) *41-51,53-56,58-62 and 64-68* is/are pending in the application.

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

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *41-51,53-56,58-60 and 64-68* 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 *4/8/10*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 41-51, 53-56, 58-62 and 64-68 are pending in this application. Claims 61 and 62 are withdrawn. Claims 41-51, 53-56, 58-60 and 64-68 are rejected.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on April 8, 2010 has been considered by the examiner. See attached 1449.

Claim Rejections - 35 USC § 102

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 –
>
> (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.

Claims 41 and 42 are rejected under 35 U.S.C. 102(b) as being anticipated by Desai et al. U.S. Patent No. 5,603,929.

Desai et al. teach an ophthalmic composition comprising bromfenac (2-amino-3-(4-bromobenzoyl)phenylacetic acid) and its ophthalmically acceptable salts, esters, amides or prodrugs thereof (column 3, lines 13-29, claims 4 and 7) and polysorbates such as tweens and tyloxapol and further comprising boric acid buffer (column 2, lines 18-44).

Claim Rejections - 35 USC § 103

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

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

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

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

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 43-51, 53-56, 58-60 and 64-68 are rejected under 35 U.S.C. 103(a) as being unpatentable over Desai et al U.S. Patent No. 5,603,929 as applied to claims 41 and 42 above, and further in view of Yanni et al. U.S. Patent No. 5,475,034 and Hellberg et al. U.S. Patent No. 5,998,465.

Desai et al. teach an ophthalmic composition comprising bromfenac (2-amino-3-(4-bromobenzoyl)phenylacetic acid) and its ophthalmically acceptable salts, esters, amides or prodrugs thereof (column 3, lines 13-29, claims 4 and 7) and polysorbates such as tweens and tyloxapol and further comprising boric acid buffer (column 2, lines 18-44). It does not teach the concentration of about 0.01% to about 0.5% w/v. Yanni et al. teach 2-amino-3-4-bromobenzoylphenylacetamide (compound 15, column 9) and teach topically administrable ophthalmic compositions such as solutions, gels or ointment in concentrations of from about 0.01 to about 0.5% preferably (column 15, lines 1-55). Yanni et al. teach tyloxapol but it does not recite the specific amount. Hellberg et al. teach tyloxapol in an ophthalmic solution comprising NSAIA moieties include bromfenac (col. 3, line 57; claim 5); examples 2 and 3 (col. 11) in an amount of 0.01 to 0.05 % w/v (see examples 2 and 3, column 11). Addressing instant claims 48, 49, 55, 56, 59 and 60 drawn to the addition of one or more additives selected from a preservative, buffer, thickener, stabilizer, chelating agent and pH controlling agent, Desai et al. teach preservatives such as boric acid (column 2, lines 18-22), and benzalkonium chloride (column 3, lines 30-35), viscosity modifying agents (thickeners) such as polyvinyl pyrrolidone (column 3, lines 46-57), chelating agents (column 3, line 43) and pH controlling agent such as sodium hydroxide (see formulation example 1,

column 4). The pH is adjusted to 7.4 (see example 1, column 4) which is encompassed by instant claim 50 drawn to a pH of from about 7 to 9. Addressing instant claim 51, drawn to a pH from about 7.5 to about 8.5, Desai teach a pH of about 7.4 as noted supra. A prima facie case of obviousness exists where the claimed ranges and prior art ranges do not overlap but are close enough that one skilled in the art would have expected them to have the same properties. *Titanium Metals Corp. of America v. Banner*, 778 F.2d 775, 227 USPQ 773 (Fed. Cir. 1985). Addressing instant claim 64, Desai et al. teach an ophthalmic composition comprising bromfenac (2-amino-3-(4-bromobenzoyl)phenylacetic acid) and its ophthalmically acceptable salts, esters, amides or prodrugs thereof (column 3, lines 13-29, claims 4 and 7) and tyloxapol and further comprising boric acid buffer (a.k.a. sodium tetraborate) (column 2, lines 18-44), Benzalkonium chloride (column 3, line 34), polyvinyl pyrrolidone (column 3, line 52). It does not teach EDTA sodium salt and sodium sulfite, however, Yanni et al. teach ophthalmic solutions comprising 2-amino-3-4-bromobenzoylphenylacetamide (compound 15, column 9) and further teach incorporation of sulfites such as sodium (column 2, lines 12-14) and EDTA sodium salt (disodium EDTA) (see column 16, line 57 and column 17, line 5). It would have been obvious to employ said sodium sulfite and EDTA sodium salt in an ophthalmic formulation motivated by the teaching of Yanni et al. who disclose disodium EDTA and sodium sulfite in ophthalmic formulations of bromfenac for the purpose of stabilizing the solution (column 2, lines 2-14).

Double Patenting

Claims 41-51, 53-56, 58-60 and 64-68 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.

No claims are allowed.

Response to Arguments

Applicant's arguments with respect to claims 41-51, 53-56, 58-60 and 64-68 have been considered but are moot in view of the new ground(s) of rejection. Applicant asserts that the Hellberg reference teaches bifunctional ester compounds having both anti-inflammatory and anti-oxidant activity. The rejection has been withdrawn, however

Hellberg et al. is relied on supra for its teaching of the amount of tyloxapol incorporated into the ophthalmic solution. The double patenting rejection is maintained and hereby repeated.

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.

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, Yvonne (Bonnie) Eyler can be reached on (571) 272-0871. 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.

/YVONNE L. EYLER/
Supervisory Patent Examiner, Art Unit 1619

Donna Jagoe /D. J./
Examiner
Art Unit 1619

June 15, 2010

Notice of References Cited	Application/Control No. 10/525,006	Applicant(s)/Patent Under Reexamination SAWA ET AL.	
	Examiner Donna Jagoe	Art Unit 1619	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
*	A	US-5,603,929	02-1997	Desai et al.	424/78.04
*	B	US-5,475,034	12-1995	Yanni et al.	514/619
	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
	Jagoe, Donna	1619

SEARCHED

Class	Subclass	Date	Examiner
514	567	5/30/09	dj
424	486	5/30/09	dj
	updated	12/17/09	dj
	updated search	6/15/10	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
WEST see attached search history transcript	12/17/09	dj
WEST 2.5.1 see attached search history transcript	6/15/10	dj

INTERFERENCE SEARCH

Class	Subclass	Date	Examiner

/Donna Jagoe/ Examiner.Art Unit 1619	

Sheet 1 of 1

INFORMATION DISCLOSURE STATEMENT

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

U.S. DEPARTMENT OF COMMERCE
PATENT AND TRADEMARK OFFICE

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

Date Submitted to PTO: April 8, 2010

ATTY DOCKET NO. 2005_0232A	**SERIAL NO.** 10/525,006
APPLICANT Shirou SAWA et al.	
FILING DATE March 28, 2005	**GROUP** 1614

U.S. PATENT DOCUMENTS

*EXAMINER INITIAL		DOCUMENT NUMBER	DATE	NAME	CLASS	SUBCLASS	FILING DATE IF APPROPRIATE
/D.J./	AA	6,395,746	5/2002	Cagle et al.			
	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.*)

/D.J./	CA	http://medical-dictionary.thefreedictionary.com/prophylactic accessed 12/15/2009.
	CB	
	CC	
	CD	

EXAMINER	/Donna Jagoe/ (06/14/2010)	DATE CONSIDERED

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

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NEWS	6	FEB 16	New FASTA Display Formats Added to USGENE and PCTGEN
NEWS	7	FEB 16	INPADOCDB and INPAFAMDB Enriched with New Content and Features
NEWS	8	FEB 16	INSPEC Adding Its Own IPC codes and Author's E-mail Addresses
NEWS	9	APR 02	CAS Registry Number Crossover Limits Increased to 500,000 in Key STN Databases
NEWS	10	APR 02	PATDPAFULL: Application and priority number formats enhanced
NEWS	11	APR 02	DWPI: New display format ALLSTR available
NEWS	12	APR 02	New Thesaurus Added to Derwent Databases for Smooth Sailing through U.S. Patent Codes
NEWS	13	APR 02	EMBASE Adds Unique Records from MEDLINE, Expanding Coverage back to 1948
NEWS	14	APR 07	CA/CAplus CLASS Display Streamlined with Removal of Pre-IPC 8 Data Fields
NEWS	15	APR 07	50,000 World Traditional Medicine (WTM) Patents Now Available in CAplus
NEWS	16	APR 07	MEDLINE Coverage Is Extended Back to 1947

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=> FIL REGISTRY

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	0.22	0.22

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Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

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DICTIONARY FILE UPDATES: 13 JUN 2010 HIGHEST RN 1227570-00-4

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TSCA INFORMATION NOW CURRENT THROUGH January 8, 2010.

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http://www.cas.org/support/stngen/stndoc/properties.html

=> s 91714-92-2/rn
L1 0 91714-92-2/RN

=> s 91714-94-2/rn
L2 1 91714-94-2/RN

=> d l2

L2 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2010 ACS on STN
RN **91714-94-2** REGISTRY
ED Entered STN: 16 Nov 1984
CN Benzeneacetic acid, 2-amino-3-(4-bromobenzoyl)- (CA INDEX NAME)
OTHER NAMES:
CN AHR 10282
CN Bromfenac
CN Xibrom

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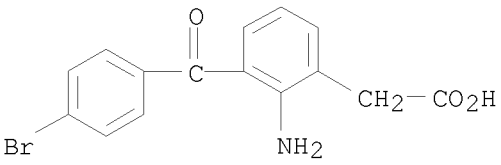
CN [2-Amino-3-(p-bromobenzoyl)phenyl]acetic acid
MF C15 H12 Br N O3
CI COM
LC STN Files: ADISINSIGHT, ADISNEWS, BIOSIS, BIOTECHNO, CA, CAPLUS, CHEMCATS, CIN, CSCHEM, DDFU, DRUGU, EMBASE, IMSDRUGNEWS, IMSPATENTS, IMSPRODUCT, IMSRESEARCH, IPA, MEDLINE, MRCK*, PROMT, PROUSDDR, PS, RTECS*, SYNTHLINE, TOXCENTER, USAN, USPAT2, USPATFULL
(*File contains numerically searchable property data)
Other Sources: WHO



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

227 REFERENCES IN FILE CA (1907 TO DATE)
27 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
230 REFERENCES IN FILE CAPLUS (1907 TO DATE)

=> s tyloxapol/cn
L3 1 TYLOXAPOL/CN

=> d l3

L3 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2010 ACS on STN
RN 25301-02-4 REGISTRY
ED Entered STN: 16 Nov 1984
CN Formaldehyde, polymer with oxirane and 4-(1,1,3,3-tetramethylbutyl)phenol (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Ethylene oxide, polymer with formaldehyde and p-(1,1,3,3-tetramethylbutyl)phenol (8CI)
CN Oxirane, polymer with formaldehyde and 4-(1,1,3,3-tetramethylbutyl)phenol (9CI)
CN Phenol, 4-(1,1,3,3-tetramethylbutyl)-, polymer with formaldehyde and oxirane (9CI)
CN Phenol, p-(1,1,3,3-tetramethylbutyl)-, polymer with ethylene oxide and formaldehyde (8CI)
OTHER NAMES:
CN Alevaire
CN Ethylene oxide-formaldehyde-4-(1,1,3,3-tetramethylbutyl)phenol copolymer
CN Ethylene oxide-formaldehyde-p-octylphenol copolymer
CN NSC 90255
CN Oxyethylated tertiary octyl-phenol-formaldehyde polymer
CN p-Isooctylpolyoxyethylenephenol formaldehyde polymer
CN Superinone
CN Triton A 20

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CN Triton WR 1339
CN **Tyloxapol**
DR 9014-50-0, 9014-66-8, 9015-10-5
MF (C14 H22 O . C2 H4 O . C H2 O)x
CI PMS, COM
PCT Phenolic resin, Polyether, Polyether formed
LC STN Files: ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, BIOSIS, BIOTECHNO, CA, CAPLUS, CASREACT, CHEMCATS, CHEMLIST, CIN, CSCHEM, DDFU, DRUGU, EMBASE, IPA, MEDLINE, MRCK*, PATDPASPC, PROMT, PS, RTECS*, TOXCENTER, USAN, USPAT2, USPATFULL, USPATOLD, VETU
(*File contains numerically searchable property data)
Other Sources: DSL**, WHO
(**Enter CHEMLIST File for up-to-date regulatory information)

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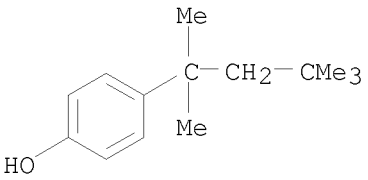
CRN 140-66-9
CMF C14 H22 O

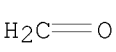


CM 2

CRN 75-21-8
CMF C2 H4 O

CM 3

CRN 50-00-0
CMF C H2 O



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

844 REFERENCES IN FILE CA (1907 TO DATE)
4 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA

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844 REFERENCES IN FILE CAPLUS (1907 TO DATE)

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=> file medicine
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COST IN U.S. DOLLARS                        SINCE FILE      TOTAL
                                               ENTRY    SESSION
FULL ESTIMATED COST                            10.68      10.90

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FILE 'LIFESCI' ENTERED AT 16:01:31 ON 14 JUN 2010

FILE 'MEDLINE' ENTERED AT 16:01:31 ON 14 JUN 2010

FILE 'NAPRALERT' ENTERED AT 16:01:31 ON 14 JUN 2010

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FILE 'USPATFULL' ENTERED AT 16:01:31 ON 14 JUN 2010

FILE 'USPATOLD' ENTERED AT 16:01:31 ON 14 JUN 2010

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=> s l1 and l2
'RN' IS NOT A VALID FIELD CODE
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L4 0 L1 AND L2

=> s bromfenac and tyloxapol
L5 150 BROMFENAC AND TYLOXAPOL

=> s ophthalmic
L6 263335 OPHTHALMIC

=> s l5 and l6
L7 111 L5 AND L6

=> dup rem
ENTER L# LIST OR (END):l7
DUPLICATE IS NOT AVAILABLE IN 'ADISINSIGHT, ADISNEWS, DGENE, DRUGMONOG2,
IMSPRODUCT, KOSMET, PCTGEN, USGENE'.
ANSWERS FROM THESE FILES WILL BE CONSIDERED UNIQUE
PROCESSING COMPLETED FOR L7
L8 106 DUP REM L7 (5 DUPLICATES REMOVED)

=> s l8 and pd<2004
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8 FILES SEARCHED...
'2004' NOT A VALID FIELD CODE
'2004' NOT A VALID FIELD CODE
15 FILES SEARCHED...
'2004' NOT A VALID FIELD CODE
22 FILES SEARCHED...
'2004' NOT A VALID FIELD CODE
27 FILES SEARCHED...
29 FILES SEARCHED...
L9 38 L8 AND PD<2004

=> s bromfenac sodium or bromfenac monosodium
L10 496 BROMFENAC SODIUM OR BROMFENAC MONOSODIUM

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=> s tyloxapol or alevaire or superinone or triton A 20 or triton WR 1339
   5 FILES SEARCHED...
THE ESTIMATED SEARCH COST FOR FILE 'CAPLUS' IS 20.79 U.S. DOLLARS
DO YOU WANT TO CONTINUE WITH THIS REQUEST? (Y)/N or END:s l10 and l11

DO YOU WANT TO CONTINUE WITH THIS REQUEST? (Y)/N or END:y
   8 FILES SEARCHED...
  25 FILES SEARCHED...
  30 FILES SEARCHED...
  31 FILES SEARCHED...
L11       9953 TYLOXAPOL OR ALEVAIRE OR SUPERINONE OR TRITON A 20 OR TRITON WR
               1339

=>

=> s l10 and l11
   5 FILES SEARCHED...
L12          8 L10 AND L11

=> dup rem
ENTER L# LIST OR (END):l12
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IMSPRODUCT, KOSMET, PCTGEN, USGENE'.
ANSWERS FROM THESE FILES WILL BE CONSIDERED UNIQUE
PROCESSING COMPLETED FOR L12
L13           5 DUP REM L12 (3 DUPLICATES REMOVED)

=> d l13 1-5 ibib, kwic

L13  ANSWER 1 OF 5  USPATFULL on STN
ACCESSION NUMBER:       2008:362814  USPATFULL
TITLE:                  Transdermal Drug Delivery Formulation
INVENTOR(S):            Singh, Jagat, Scarborough, CANADA
PATENT ASSIGNEE(S):     NUVO RESEARCH INC., MISSISSAUGA, CANADA (non-U.S.
                        corporation)

                             NUMBER       KIND    DATE
                        ---------------- ------ --------
PATENT INFORMATION:     US 20080319092     A1   20081225
APPLICATION INFO.:      US 2006-3028       A1   20060804  (12)
                        WO 2006-CA1271          20060804
                                                20080728  PCT 371 date

                               NUMBER             DATE
                        -------------------     --------
PRIORITY INFORMATION:   US 2005-705498P         20050805 (60)
                        US 2006-771030P         20060208 (60)
DOCUMENT TYPE:          Utility
FILE SEGMENT:           APPLICATION
LEGAL REPRESENTATIVE:   KATTEN MUCHIN ROSENMAN LLP, (C/O PATENT ADMINISTRATOR),
                        2900 K STREET NW, SUITE 200, WASHINGTON, DC,
                        20007-5118, US
NUMBER OF CLAIMS:       2
```

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EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 3 Drawing Page(s)
LINE COUNT: 2115
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
DETD . . . Aminobenzoate Sodium; Anidoxime; Anileridine; Anileridine Hydrochloride; Anilopam Hydrochloride; Anirolac; Antipyrine; Aspirin; Benoxaprofen; Benzydamine Hydrochloride; Bicifadine Hydrochloride; Brifentanil Hydrochloride; Bromadoline Maleate; **Bromfenac Sodium**; Buprenorphine Hydrochloride; Butacetin; Butixirate; Butorphanol; Butorphanol Tartrate; Carbamazepine; Carbaspirin Calcium; Carbiphene Hydrochloride; Carfentanil Citrate; Ciprefadol Succinate; Ciramadol; Ciramadol Hydrochloride; Clonixeril;. . .
DETD . . . Trioxsalen; Triptorelin Pamoate; Trolamine Polypeptide Oleate Condensate; Trombodipine; Trometarnol; Tromethamine; Tropine Ester; Trospectomycin; Trovafloxacin; Trovafloxacin Mesylate; Trovirdine; Tucaresol; Tulobuterol; Tylogenin; **Tyloxapol**; Undecoylium Chloride; Undecoylium Chloride Iodine Complex; Unoprostone Isopropyl; Urapidil; Urea, C-13; Urea, C-14; Uridine Triphosphate; Valaciclovir; Valdecoxib; Valganciclovir Hydrochloride; Valproate. . .

L13 ANSWER 2 OF 5 CAPLUS COPYRIGHT 2010 ACS on STN DUPLICATE 1
ACCESSION NUMBER: 2007:1421955 CAPLUS
DOCUMENT NUMBER: 148:39746
TITLE: Bromfenac ophthalmic formulations and methods of use
INVENTOR(S): Sawa, Shirou; Fujita, Shuhei; Grillone, Lisa R.
PATENT ASSIGNEE(S): Ista Pharmaceuticals, Inc., USA
SOURCE: U.S. Pat. Appl. Publ., 21pp., Cont.-in-part of U.S. Ser. No. 525,006.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
US 20070287749	A1	20071213	US 2007-755662		20070530
US 20050239895	A1	20051027	US 2005-525006		20050328
PRIORITY APPLN. INFO.:			JP 2003-12427	A	20030121
			US 2005-525006	A2	20050328
			WO 2004-JP350	W	20040116

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
AB . . . 2-amino-3-(4-bromobenzoyl)phenylacetic acid or its pharmacol. acceptable salt or a hydrate thereof, an alkyl aryl polyether alc. type polymer such as **tyloxapol**, or a polyethylene glycol fatty acid ester such as polyethylene glycol monostearate. The present invention further discloses new bromfenac ophthalmic. . .
IT 25301-02-4, **Tyloxapol** 25322-68-3D, Polyethylene glycol, esters
RL: MOA (Modifier or additive use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(bromfenac ophthalmic formulations and methods of use)
IT 91714-93-1, **Bromfenac sodium** 91714-94-2, Bromfenac
RL: PEP (Physical, engineering or chemical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)

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(bromfenac ophthalmic formulations and methods of use)

L13 ANSWER 3 OF 5 USPATFULL on STN

ACCESSION NUMBER:	2007:308290 USPATFULL		
TITLE:	Penetration Enhancer Combinations for Transdermal Delivery		
INVENTOR(S):	Mitragotri, Samir, Goleta, CA, UNITED STATES Karande, Pankaj S., Somerville, MA, UNITED STATES Jain, Amit K., Redwood City, CA, UNITED STATES		
	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20070269379	A1	20071122
APPLICATION INFO.:	US 2004-560571	A1	20040721 (10)
	WO 2004-US23634		20040721 20070202 PCT 371 date
	NUMBER		DATE
PRIORITY INFORMATION:	US 2003-560717P		20030723 (60)
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	APPLICATION		
LEGAL REPRESENTATIVE:	Rober Berliner, Berliner & Associated, 555 W. Fifth Street, 31st Floor, Los Angeles, CA, 90013, US		
NUMBER OF CLAIMS:	52		
EXEMPLARY CLAIM:	1		
NUMBER OF DRAWINGS:	18 Drawing Page(s)		
LINE COUNT:	4179		

DETD . . . Aminobenzoate Sodium; Amidoxime; Anileridine; Anileridine Hydrochloride; Anilopam Hydrochloride; Anirolac; Antipyrine; Aspirin; Benoxaprofen; Benzydamine Hydrochloride; Bicifadine Hydrochloride; Brifentanil Hydrochloride; Bromadoline Maleate; **Bromfenac Sodium**; Buprenorphine Hydrochloride; Butacetin; Butixirate; Butorphanol; Butorphanol Tartrate; Carbamazepine; Carbaspirin Calcium; Carbiphene Hydrochloride; Carfentanil Citrate; Ciprefadol Succinate; Ciramadol; Ciramadol Hydrochloride; Clonixeril;. . .

DETD . . . Trioxsalen; Triptorelin Pamoate; Trolamine Polypeptide Oleate Condensate; Trombodipine; Trometarnol; Tromethamine; Tropine Ester; Trospectomycin; Trovafloxacin; Trovafloxacin Mesylate; Trovirdine; Tucaresol; Tulobuterol; Tylogenin; **Tyloxapol**; Undecoylium Chloride; Undecoylium Chloride Iodine Complex; Unoprostone Isopropyl; Urapidil; Urea, C-13; Urea, C-14; Uridine Triphosphate; Valaciclovir; Valdecoxib; Valganciclovir Hydrochloride; Valproate. . .

L13 ANSWER 4 OF 5 USPATFULL on STN

ACCESSION NUMBER:	2007:95155 USPATFULL		
TITLE:	Aqueous solution preparation containing aminoglycoside antibiotic and bromfenac		
INVENTOR(S):	Sawa, Shirou, 366-1-105, MINAMIBEFU 4-CHOME, NISHI-KU, KOBE-SHI, HYOGO, JAPAN 651-2116		
	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20070082857	A1	20070412

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APPLICATION INFO.:	US 2004-578359	A1	20041112	(10)
	WO 2004-JP16849		20041112	
			20060606	PCT 371 date

	NUMBER	DATE
PRIORITY INFORMATION:	JP 2003-384646	20031114

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: WENDEROTH, LIND & PONACK, L.L.P., 2033 K STREET N. W., SUITE 800, WASHINGTON, DC, 20006-1021, US
NUMBER OF CLAIMS: 8
EXEMPLARY CLAIM: 1
LINE COUNT: 807
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM The nonionic surfactant includes, for example, polyoxyethylene sorbitan fatty acid esters (e.g. polysorbate 20, polysorbate 60, polysorbate 80, etc.); **tyloxapol**; polyoxyl 40 monostearate; polyoxyethylene hydrogenated castor oil (e.g. polyoxyethylene (40) hydrogenated castor oil, polyoxyethylene (60) hydrogenated castor oil, etc.); poloxamer; and the like. Preferable examples of the nonionic surfactant are polysorbate 80, **tyloxapol** or polyoxyl 40 monostearate.

SUMM . . . polymer (e.g. povidone K-30, polyvinyl alcohol, α-cyclodextrin, etc.); citric acid or its pharmacologically acceptable salt and a nonionic surfactant (e.g. **tyloxapol**, polysorbate 80, polyoxyl 40 monostearate, etc.); monoethanolamine or its pharmacologically acceptable salt and a nonionic water-soluble polymer (e.g. povidone K-30, polyvinyl alcohol, α-cyclodextrin, etc.); monoethanolamine or its pharmacologically acceptable salt and a nonionic surfactant (e.g. **tyloxapol**, polysorbate 80, polyoxyl 40 monostearate, etc.); N-methylglucamine or its pharmacologically acceptable salt and a nonionic water-soluble polymer (e.g. povidone K-30, polyvinyl alcohol, α-cyclodextrin, etc.); N-methylglucamine or its pharmacologically acceptable salt and a nonionic surfactant (e.g. **tyloxapol**, polysorbate 80; polyoxyl 40 monostearate, etc.); nicotinamide and a nonionic water-soluble polymer (e.g. povidone K-30, polyvinyl alcohol, α-cyclodextrin, etc.); nicotinamide and a nonionic surfactant (e.g. **tyloxapol**, polysorbate 80, polyoxyl 40 monostearate, etc.); a nonionic surfactant (e.g. **tyloxapol**, polysorbate 80, polyoxyl 40 monostearate, etc.) and a nonionic water-soluble polymer (e.g. povidone K-30, polyvinyl alcohol, α-cyclodextrin, etc.), or the. . .

SUMM . . . purified water or water for injections), and to this solution were added an aminoglycoside antibiotic (e.g. gentamicin sulfate, etc.) and **bromfenac sodium**. The mixture was dissolved and adjusted to a pH of about not less than 7.0, preferably to a pH of. . .

SUMM . . . solvent, thereby to prepare a solution. To the solution were added an aminoglycoside antibiotic (e.g. tobramycin, gentamicin sulfate, etc.) and **bromfenac sodium**, and the resulting solution was adjusted to a pH of about not less than 7.0, preferably 7.5 to 8.5.

SUMM . . . above, thereby to prepare a solution. To the solution were added an aminoglycoside antibiotic (e.g. tobramycin, gentamicin sulfate,

etc.) and **bromfenac sodium**, and the resulting solution was adjutsted to a pH of about not less than 6.0, preferably 7.5 to 8.5.

SUMM . . . example, blepharitis, hordeolum, conjunctivitis, keratitis, dacryocystitis, etc. The dose in the case where an eye drop comprising 0.1 w/v % **bromfenac sodium** hydrate and 0.3 w/v % tobramycin or 0.3 w/v % gentamicin sulfate is applied may be 1 to 2 drops. . .

SUMM In the case where the aqueous solution preparation of the present invention comprising, for example, 0.1 w/v % **bromfenac sodium** hydrate and 0.3 w/v % tobramycin or 0.3 w/v % gentamicin sulfate is applied in the form of a nose. . .

SUMM In the case where the aqueous solution preparation of the present invention comprising, for example, 0.1 w/v % **bromfenac sodium** hydrate and 0.3 w/v % tobramycin or 0.3 w/v % gentamicin sulfate is applied in the form of an ear. . .

SUMM . . . various infectious diseases by the aqueous solution preparation of the present invention, an injection comprising, for example, 0.1 w/v % **bromfenac sodium** hydrate and 0.3 w/v % tobramycin or 0.3 w/v % gentamicin sulfate may be applied intramuscularly or subcutaneously in an. . .

DETD . . . 1 was prepared by dissolving boric acid and borax in a fixed amount of purified water and adding tobramycin and **bromfenac sodium** to the solution, followed by dissolution. With respect to the formulation 2, sodium citrate was further added to the formulation. . . was prepared by dissolving boric acid and borax in a fixed amount of purified water and adding gentamicin sulfate and **bromfenac sodium** thereto to make a solution. Then, the pH values of these formulations were adjusted by addition of hydrochloric acid and. . .

DETD A combination solution comprising tobramycin and **bromfenac sodium** as shown in Table 3 was prepared (formulation 4). Boric acid and borax were added to and dissolved in a fixed amount of purified water, and to this solution were added tobramycin and **bromfenac sodium**, followed by dissolution. Separately, each additive was added to and dissolved in the prescribed amount of purified water to give. . . determined according to the criteria as described in Example 1.

TABLE 3

Formulation of combination solution

Component	Formulation 4 w/v %
Bromfenac sodium	0.2
Tobramycin	0.6
Boric acid	1.14
Borax	4.5
Hydrochloric acid	q.s.
Sodium hydroxide	q.s.
Purified water	q.s.
. . . sorbate	0.4
Sodium glutamate	0.6
N-Methyl-2-pyrrolidone	2.0

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Povidone K-30	4.0
Sodium alginate	0.2
Sodium chondroitin sulfate	2.0
Polysorbate 80	0.6
Tyloxapol	0.6
Polyoxyl 40 monostearate	0.6
Benzalkonium chloride	0.2
Sodium lauryl sulfate	0.2

DETD . . . alginate 0.1 w/v % strongly turbid

Sodium chondroitin sulfate 1.0 w/v % strongly turbid

Polysorbate 80 0.3 w/v % clear

Tyloxapol 0.3 w/v % clear

Polyoxyl 40 monostearate 0.3 w/v % clear

Benzalkonium chloride 0.1 w/v % strongly turbid

Sodium lauryl. . .

DETD . . . monoethanolamine and N-methylglucamine; nicotinamide; a nonionic water-soluble polymer such as povidone K-30; or a nonionic surfactant such as polysorbate 80, **tyloxapol**, and polyoxyl 40 monostearate.

DETD Combination solutions comprising gentamicin sulfate and **bromfenac sodium** as shown in Table 6 were prepared (formulations 5 and 6). The formulation 5 was prepared by adding sodium dihydrogen phosphate and concentrated glycerine to a fixed amount of purified water, dissolving the mixture, and adding gentamicin sulfate and **bromfenac sodium** thereto, followed by dissolution. With respect to the formulation 6, boric acid and borax was added to and dissolved in a fixed amount of purified water, and to this solution were added gentamicin sulfate and **bromfenac sodium**, and then the mixture was dissolved. Separately, each additive solution was prepared as shown in Table 7. Each additive was. . . to the criteria as described in Example 1.

TABLE 6

Component	Formulation of combination solution (w/v %) Formulation 5	Formulation 6
Bromfenac sodium	0.2	0.2
Gentamicin sulfate	0.6	0.6
Boric acid	--	1.14
Borax	--	4.5
Sodium dihydrogen phosphate	0.2	--
Concentrated glycerine	5.2	--
Hydrochloric acid	q.s.	q.s.

Sodium. . .

DETD . . . 2.0

Nicotinamide	2.0
Potassium sorbate	0.4
Povidone K-30	4.0
Polyvinyl alcohol	2.0

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α-Cyclodextrin	4.0			
Sodium alginate	0.2			
Polysorbate 80	0.6			
Tyloxapol	0.6			
Polyoxyl 40 monostearate	0.6			
Benzalkonium chloride	0.2			
Sodium lauryl sulfate	0.2			

DETD . . . 6.0 Clear

Sodium alginate	0.1	Formulation 6	6.5	Strongly turbid
Polysorbate 80	0.3	Formulation 6	6.5	Clear
Polysorbate 80	0.3	Formulation 6	6.0	Clear
Tyloxapol	0.3	Formulation 6	6.5	Clear
Polyoxyl 40 monostearate	0.3	Formulation 6	6.5	Clear
Benzalkonium chloride	0.1	Formulation 6	6.5	Strongly turbid
Sodium lauryl	0.1	Formulation. . .		

DETD . . . nicotinamide; a nonionic water-soluble polymer such as povidone, polyvinyl alcohol, and α-cyclodextrin; or a nonionic surfactant such as polysorbate 80, **tyloxapol**, and polyoxyl 40 monostearate. Furthermore, when α-cyclodextrin as a nonionic water-soluble polymer, or polysorbate 80 as a nonionic surfactant was. . .

DETD
TABLE 9

Bromfenac sodium 3/2 hydrate	0.1	g
Tobramycin	0.3	g
Boric acid	1.4	g
Borax	0.8	g
Hydrochloric acid	q.s.	
Purified water	q.s.	

. . .

DETD Borax was dissolved in about 80 ml of purified water. Tobramycin and **bromfenac sodium** were added to the solution, and the mixture was dissolved. To the solution was added boric acid, and the mixture. . .

DETD
TABLE 10

Bromfenac sodium 3/2 hydrate	0.1	g
Tobramycin	0.3	g
Boric acid	1.8	g
Sodium citrate	0.3	g
Sodium hydroxide	q.s.	
Purified water. . .		

DETD Tobramycin and **bromfenac sodium** were added to and dissolved in about 80 ml of purified water. To the solution were added sodium citrate and. . .

DETD
TABLE 11

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Bromfenac sodium 3/2 hydrate	0.1	g
Gentamicin sulfate	0.3	g
Polysorbate 80	0.3	g
Sodium dihydrogen phosphate	0.1	g
Concentrated glycerine	2.6. . .	

DETD . . . were added to and dissolved in about 80 ml of purified water. To the solution were added gentamicin sulfate and **bromfenac sodium**, and the mixture was dissolved. Sodium hydroxide was added to the solution to adjust the pH, and purified water was. . .

DETD

TABLE 12

Bromfenac sodium 3/2 hydrate	0.1	g
Tobramycin	0.3	g
Boric acid	1.6	g
Povidone K-30	2.0	g
Sodium hydroxide	q.s.	
Purified water. . .		

DETD Tobramycin and **bromfenac sodium** were added to and dissolved in about 80 ml of purified water. To the solution were added povidone K-30 and. . .

DETD

TABLE 13

Bromfenac sodium 3/2 hydrate	0.1	g
Tobramycin	0.3	g
Boric acid	1.6	g
N-Methylglucamine	1.0	g
Sodium hydroxide	q.s.	
Purified water	q.s.	

. . .

DETD Tobramycin and **bromfenac sodium** were added to and dissolved in about 80 ml of purified water. To the solution were added N-methylglucamine and boric. . .

DETD

TABLE 14

Bromfenac sodium 3/2 hydrate	0.1	g
Tobramycin	0.3	g
Boric acid	1.6	g
Borax	0.6	g
Povidone K-30	1.0	g
N-Methylglucamine	0.1. . .	

DETD Tobramycin and **bromfenac sodium** were added to and dissolved in about 80 ml of purified water. To the solution were added povidone K-30, N-methylglucamine,. . .

DETD

TABLE 15

Jagoe

Bromfenac sodium 3/2 hydrate	0.1	g
Tobramycin	0.3	g
Boric acid	1.6	g
Borax	0.7	g
Benzalkonium chloride	0.005	g
Tyloxapol	0.02	g
Povidone K-30	1.0	g
Sodium edetate	0.02	g
Sodium hydroxide	q.s.	
Purified water	q.s.	
Total volume	100	ml

. . .

DETD Tobramycin and **bromfenac sodium** were added to and dissolved in about 80 ml of purified water. To the solution were added **tyloxapol**, povidone K-30, sodium edetate, benzalkonium chloride, boric acid and borax, and the mixture was dissolved. The pH of the solution. . .

DETD . . . it is possible to obtain a clear aqueous solution preparation comprising an aminoglycoside antibiotic or its pharmacologically acceptable salt and **bromfenac sodium** or its pharmacologically acceptable salt.

IT 68-04-2, Sodium citrate 77-92-9, Citric acid, biological studies 98-92-0, Nicotinic acid amide 141-43-5, Monoethanolamine, biological studies 1403-66-3, Gentamicin 1405-41-0, Gentamicin sulfate 6284-40-8, N-Methylglucamine 32986-56-4, Tobramycin 91714-93-1, **Bromfenac sodium** 91714-94-2
(aqueous solns. containing aminoglycoside antibiotic and bromfenac)

L13 ANSWER 5 OF 5 CAPLUS COPYRIGHT 2010 ACS on STN DUPLICATE 2
ACCESSION NUMBER: 2006:439980 CAPLUS
DOCUMENT NUMBER: 144:440131
TITLE: Aqueous eye drops with accelerated intraocular migration
INVENTOR(S): Sawa, Shirou; Fujimoto, Tomoko
PATENT ASSIGNEE(S): Senju Pharmaceutical Co., Ltd., Japan
SOURCE: PCT Int. Appl., 40 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2006049250	A1	20060511	WO 2005-JP20302	20051104

W: 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, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW

RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE,

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             IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ,
             CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH,
             GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY,
             KG, KZ, MD, RU, TJ, TM
     CA 2560559           A1    20060511    CA 2005-2560559        20051104
     CN 1993118           A     20070704    CN 2005-80025963       20051104
     EP 1808170           A1    20070718    EP 2005-805529         20051104
         R:  AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE,
             IS, IT, LI, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR
     US 20070021507       A1    20070125    US 2006-568418         20060426
     IN 2006KN02763       A     20070601    IN 2006-KN2763         20060921
     MX 2007001172        A     20070312    MX 2007-1172           20070129
PRIORITY APPLN. INFO.:                      JP 2004-322569      A  20041105
                                            WO 2005-JP20302     W  20051104
ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
REFERENCE COUNT:         18    THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS
                               RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT
AB   .  .  .  inflammatory diseases on the external segment or anterior segment
     of the eye.  For example, an aqueous eye drop solution contained
     bromfenac sodium hydrate 0.1, aminoethylsulfonic acid
     0.5, benzalkonium chloride 0.005, tyloxapol 0.02, povidone 2,
     sodium edetate 0.02, boric acid 1.3, borax 0.74, NaOH q.s., and distilled
     water balance to 100 %.


=> d his

     (FILE 'HOME' ENTERED AT 15:59:56 ON 14 JUN 2010)

     FILE 'REGISTRY' ENTERED AT 16:00:17 ON 14 JUN 2010
L1             0 S 91714-92-2/RN
L2             1 S 91714-94-2/RN
L3             1 S TYLOXAPOL/CN

     FILE 'ADISCTI, ADISINSIGHT, ADISNEWS, BIOSIS, BIOTECHNO, CAPLUS, DDFB,
     DGENE, DISSABS, DRUGB, DRUGMONOG2, DRUGU, EMBAL, EMBASE, ESBIOBASE,
     IFIPAT, IMSDRUGNEWS, IMSPRODUCT, IPA, KOSMET, LIFESCI, MEDLINE,
     NAPRALERT, NLDB, PASCAL, PCTGEN, SCISEARCH, TOXCENTER, ...' ENTERED AT
     16:01:31 ON 14 JUN 2010
L4             0 S L1 AND L2
L5           150 S BROMFENAC AND TYLOXAPOL
L6        263335 S OPHTHALMIC
L7           111 S L5 AND L6
L8           106 DUP REM L7 (5 DUPLICATES REMOVED)
L9            38 S L8 AND PD<2004
L10          496 S BROMFENAC SODIUM OR BROMFENAC MONOSODIUM
L11         9953 S TYLOXAPOL OR ALEVAIRE OR SUPERINONE OR TRITON A 20 OR TRITON
L12            8 S L10 AND L11
L13            5 DUP REM L12 (3 DUPLICATES REMOVED)

=> d l9 30-38 ibib, kwic

L9   ANSWER 30 OF 38  USPATFULL on STN
ACCESSION NUMBER:       1999:160081  USPATFULL
```

Jagoe

10/525006

TITLE: Esters of non-steroidal anti-flammatory carboxylic acids
INVENTOR(S): Hellberg, Mark, Arlington, TX, United States
Delgado, Pete, Fort Worth, TX, United States
Nixon, Jon C., Mansfield, TX, United States
PATENT ASSIGNEE(S): Alcon Laboratories, Inc., Fort Worth, TX, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5998465		19991207	<--
APPLICATION INFO.:	US 1998-139506		19980825 (9)	

RELATED APPLN. INFO.: Division of Ser. No. US 1998-23385, filed on 13 Feb 1998 which is a division of Ser. No. US 1995-526913, filed on 12 Sep 1995, now patented, Pat. No. US 5750564
DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Mach, D. Margaret
LEGAL REPRESENTATIVE: Mayo, Michael C.
NUMBER OF CLAIMS: 30
EXEMPLARY CLAIM: 1
LINE COUNT: 786
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM . . . using the compounds and compositions of the present invention to prevent and treat inflammatory disorders including ocular inflammation associated with **ophthalmic** disease and **ophthalmic** surgery.

SUMM . . . acid

indoprofen

pirprofen	clidanac	fenoprofen
naproxen	fenclorac	meclofenamate
benoxaprofen	carprofen	isofezolac
aceloferac	fenbufen	etodolic acid
fleclozic acid	amfenac	efenamic acid
bromfenac	ketoprofen	fencloenac
alcofenac	orpanoxin	zomopirac
diflunisal	pranoprofen	zaltoprofen

DETD The present invention is particularly directed to the provision of compositions adapted for treatment of **ophthalmic** tissues. The **ophthalmic** compositions of the present invention will include one or more compounds of formulas (I) and (II) and a pharmaceutically acceptable. . . semi-solid compositions. Suspensions may be preferred for compounds of formulas (I) and (II) which are relatively insoluble in water. The **ophthalmic** compositions of the present invention may also include various other ingredients, such as buffers, preservatives, co-solvents and viscosity building agents.

DETD **Ophthalmic** products are typically packaged in multidose form. Preservatives are thus required to prevent microbial contamination during use. Suitable preservatives include:. . .

DETD . . . the formulations, to decrease physical separation of components of a suspension or emulsion of formulation and/or otherwise to improve the **ophthalmic** formulation. Such viscosity building agents

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include, for example, polyvinyl alcohol, polyvinyl pyrrolidone, methyl cellulose, hydroxypropyl methylcellulose, hydroxyethyl cellulose, carboxymethyl cellulose,. . .

DETD As indicated above, use of the compounds of formulas (I)and (II) to prevent or reduce damage to **ophthalmic** tissues at the cellular level is a particularly important aspect of the present invention. **Ophthalmic** conditions which may be treated include, but are not limited to, cataracts, retinopathies, heredodegenerative diseases, macular degeneration, ocular ischemia, glaucoma, and damage associated with injuries to **ophthalmic** tissues, such as ischemia reperfusion injuries, photochemical injuries, and injuries associated with ocular surgery, particularly injuries to the retina, cornea. . . other tissues caused by exposure to light or surgical instruments. The compounds may also be used as an adjunct to **ophthalmic** surgery, such as by vitreal or subconjunctival injection following **ophthalmic** surgery. The compounds may be used for acute treatment of temporary conditions, or may be administered chronically, especially in the case of degenerative disease. The compounds may also be used prophylactically, especially prior to ocular surgery or noninvasive **ophthalmic** procedures, or other types of surgery.

DETD Topical **ophthalmic** compositions useful for treating inflammation and/or tissue oxidative damage:

DETD

Component	% w/v
Compound	0.05-5.0
Tyloxapol	0.01-0.05
HPMC	0.5
Benzalkonium Chloride	0.01
Sodium Chloride	0.8
Edetate Disodium	0.01
NaOH/HCl	q.s. pH 7.4
Purified Water	q.s. 100. . .

DETD A preferred topical **ophthalmic** composition useful for treating inflammation and/or tissue oxidative damage:

DETD

Component	% w/v
Compound E	0.10
Tyloxapol	0.01-0.05
HPMC	0.5
Benzalkonium Chloride	0.01
Sodium Chloride	0.8
Edetate Disodium	0.01
NaOH/HCl	q.s. pH 7.4
Purified Water	q.s. 100. . .

DETD . . . either dry heat or filtered. The sterilized anti-inflammatory agent is weighed aseptically and placed into a pressurized ballmill container. The **tyloxapol**, in sterilized aqueous solution form, is then added to the ballmill container. Sterilized glass balls are then added to the. . .

CLM What is claimed is:

. . . acid; indoprofen; pirprofen; clidanac; fenoprofen; naproxen; fenclorac; meclofenamate; benoxaprofen; carprofen; isofezolac;

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aceloferac; fenbufen; etodolic acid; fleclozic acid; amfenac; efenamic acid; **bromfenac**; ketoprofen; fenclofenac; alcofenac; orpanoxin; zomopirac; diflunisal; flufenamic acid; niflumic acid; mefenamic acid; pranoprofen; zaltoprofen; indomethacin; sulindac; tolmetin; suprofen; ketorolac; flurbiprofen;. . .

CLM What is claimed is:

. . . acid; indoprofen; pirprofen; clidanac; fenoprofen; naproxen; fenclorac; meclofenamate; benoxaprofen; carprofen; isofezolac; aceloferac; fenbufen; etodolic acid; fleclozic acid; amfenac; efenamic acid; **bromfenac**; ketoprofen; fenclofenac; alcofenac; orpanoxin; zomopirac; diflunisal; flufenamic acid; niflumic acid; mefenamic acid; pranoprofen; zaltoprofen; indomethacin; sulindac; tolmetin; suprofen; ketorolac; flurbiprofen;. . .

CLM What is claimed is:

24. The method according to claim 23, wherein the composition is administered to prevent or alleviate damage to **ophthalmic** tissues.

CLM What is claimed is:

. . . acid; indoprofen; pirprofen; clidanac; fenoprofen; naproxen; fenclorac; meclofenamate; benoxaprofen; carprofen; isofezolac; aceloferac; fenbufen; etodolic acid; fleclozic acid; amfenac; efenamic acid; **bromfenac**; ketoprofen; fenclofenac; alcofenac; orpanoxin; zomopirac; diflunisal; flufenamic acid; niflumic acid; mefenamic acid; pranoprofen; zaltoprofen; indomethacin; sulindac; tolmetin; suprofen; ketorolac; flurbiprofen;. . .

IT Drug delivery systems

(**ophthalmic**; preparation of esters of non-steroidal antiinflammatory agents with antioxidant activity)

L9 ANSWER 31 OF 38 USPATFULL on STN

ACCESSION NUMBER:	1999:63322 USPATFULL
TITLE:	Anti-oxidant esters of non-steroidal anti-inflammatory agents
INVENTOR(S):	Hellberg, Mark, Arlington, TX, United States Delgado, Pete, Fort Worth, TX, United States Nixon, Jon C., Mansfield, TX, United States
PATENT ASSIGNEE(S):	Alcon Laboratories, Inc., Fort Worth, TX, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5908849		19990601	<--
APPLICATION INFO.:	US 1998-23385		19980213 (9)	
RELATED APPLN. INFO.:	Division of Ser. No. US 1995-526913, filed on 12 Sep 1995, now patented, Pat. No. US 5750564			
DOCUMENT TYPE:	Utility			
FILE SEGMENT:	Granted			
PRIMARY EXAMINER:	Rotman, Alan L.			
ASSISTANT EXAMINER:	Mach, Margaret M.			
LEGAL REPRESENTATIVE:	Mayo, Michael C.			
NUMBER OF CLAIMS:	30			
EXEMPLARY CLAIM:	1			
LINE COUNT:	797			

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CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM . . . using the compounds and compositions of the present invention to prevent and treat inflammatory disorders including ocular inflammation associated with **ophthalmic** disease and **ophthalmic** surgery.

SUMM

loxoprofen	tolfenamic acid	
		indoprofen
pirprofen	clidanac	fenoprofen
naproxen	fenclorac	meclofenamate
benoxaprofen	carprofen	isofezolac
aceloferac	fenbufen	etodolic acid
fleclozic acid		
	amfenac	efenamic acid
bromfenac	ketoprofen	fenclofenac
alcofenac	orpanoxin	zomopirac
diflunisal	pranoprofen	zaltoprofen

DETD The present invention is particularly directed to the provision of compositions adapted for treatment of **ophthalmic** tissues. The **ophthalmic** compositions of the present invention will include one or more compounds of formulas (I) and (II) and a pharmaceutically acceptable. . . semi-solid compositions. Suspensions may be preferred for compounds of formulas (I) and (II) which are relatively insoluble in water. The **ophthalmic** compositions of the present invention may also include various other ingredients, such as buffers, preservatives, co-solvents and viscosity building agents.

DETD **Ophthalmic** products are typically packaged in multidose form. Preservatives are thus required to prevent microbial contamination during use. Suitable preservatives include:. . .

DETD . . . the formulations, to decrease physical separation of components of a suspension or emulsion of formulation and/or otherwise to improve the **ophthalmic** formulation. Such viscosity building agents include, for example, polyvinyl alcohol, polyvinyl pyrrolidone, methyl cellulose, hydroxypropyl methylcellulose, hydroxyethyl cellulose, carboxymethyl cellulose,. . .

DETD As indicated above, use of the compounds of formulas (I) and (II) to prevent or reduce damage to **ophthalmic** tissues at the cellular level is a particularly important aspect of the present invention. **Ophthalmic** conditions which may be treated include, but are not limited to, cataracts, retinopathies, heredodegenerative diseases, macular degeneration, ocular ischemia, glaucoma, and damage associated with injuries to **ophthalmic** tissues, such as ischemia reperfusion injuries, photochemical injuries, and injuries associated with ocular surgery, particularly injuries to the retina, cornea. . . other tissues caused by exposure to light or surgical instruments. The compounds may also be used as an adjunct to **ophthalmic** surgery, such as by vitreal or subconjunctival injection following **ophthalmic** surgery. The compounds may be used for acute treatment of temporary conditions, or may be administered chronically, especially in the case of degenerative disease. The compounds may also be used prophylactically, especially prior to ocular surgery or noninvasive **ophthalmic** procedures, or other types of surgery.

DETD Topical **ophthalmic** compositions useful for treating inflammation and/or tissue oxidative damage:

Component	% w/v
Compound	0.05-5.0
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HPMC	0.5
Benzalkonium Chloride	0.01
Sodium Chloride	0.8
Edetate Disodium	0.01
NaOH/HCl	q.s. pH 7.4
Purified Water	q.s. 100 mL

DETD A preferred topical **ophthalmic** composition useful for treating inflammation and/or tissue oxidative damage:

Component	% w/v
Compound E	0.10
Tyloxapol	0.01-0.05
HPMC	0.5
Benzalkonium Chloride	0.01
Sodium Chloride	0.8
Edetate Disodium	0.01
NaOH/HCl	q.s. pH 7.4
Purified Water	q.s. 100 mL

DETD . . . either dry heat or filtered. The sterilized anti-inflammatory agent is weighed aseptically and placed into a pressurized ballmill container. The **tyloxapol**, in sterilized aqueous solution form, is then added to the ballmill container. Sterilized glass balls are then added to the. . .

CLM What is claimed is:

. . . acid; indoprofen; pirprofen; clidanac; fenoprofen; naproxen; fenclorac; meclofenamate; benoxaprofen; carprofen; isofezolac; aceloferac; fenbufen; etodolic acid; fleclozic acid; amfenac; efenamic acid; **bromfenac**; ketoprofen; fenclofenac; alcofenac; orpanoxin; zomopirac; diflunisal; flufenamic acid; niflumic acid; mefenamic acid; pranoprofen; zaltoprofen; indomethacin; sulindac; tolmetin; suprofen; ketorolac; flurbiprofen;. . .

CLM What is claimed is:

. . . acid; indoprofen; pirprofen; clidanac; fenoprofen; naproxen; fenclorac; meclofenamate; benoxaprofen; carprofen; isofezolac; aceloferac; fenbufen; etodolic acid; fleclozic acid; amfenac; efenamic acid; **bromfenac**; ketoprofen; fenclofenac; alcofenac; orpanoxin; zomopirac; diflunisal; flufenamic acid; niflumic acid; mefenamic acid; pranoprofen; zaltoprofen; indomethacin; sulindac; tolmetin; suprofen; ketorolac; flurbiprofen;. . .

CLM What is claimed is:

24. The method according to claim 23, wherein the composition is administered to prevent or alleviate damage to **ophthalmic** tissues.

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CLM What is claimed is:
. . . acid; indoprofen; pirprofen; clidanac; fenoprofen; naproxen; fenclorac; meclofenamate; benoxaprofen; carprofen; isofezolac; aceloferac; fenbufen; etodolic acid; fleclozic acid; amfenac; efenamic acid; **bromfenac**; ketoprofen; fenclofenac; alcofenac; orpanoxin; zomopirac; diflunisal; flufenamic acid; niflumic acid; mefenamic acid; pranoprofen; zaltoprofen; indomethacin; sulindac; tolmetin; suprofen; ketorolac; flurbiprofen;. . .
IT Drug delivery systems
(**ophthalmic**; preparation of esters of non-steroidal antiinflammatory agents with antioxidant activity)

L9 ANSWER 32 OF 38 USPATFULL on STN
ACCESSION NUMBER: 1998:51640 USPATFULL
TITLE: Anti-oxidant esters of non-steroidal anti-inflammatory agents
INVENTOR(S): Hellberg, Mark, 52211 Overridge Dr., Arlington, TX, United States 76017
Delgado, Pete, 4315 N. Segura Ct., Fort Worth, TX, United States 76132
Nixon, Jon C., 1616 Hastings Dr., Mansfield, TX, United States 76132

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5750564		19980512	<--
APPLICATION INFO.:	US 1995-526913		19950912	(8)

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Richter, Johann
ASSISTANT EXAMINER: Stockton, Laura L.
LEGAL REPRESENTATIVE: Mayo, Michael C.
NUMBER OF CLAIMS: 30
EXEMPLARY CLAIM: 1
LINE COUNT: 744
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM . . . using the compounds and compositions of the present invention to prevent and treat inflammatory disorders including ocular inflammation associated with **ophthalmic** disease and **ophthalmic** surgery.
SUMM

loxoprofen tolfenamic acid
indoprofen
pirprofen clidanac fenoprofen
naproxen fenclorac meclofenamate
benoxaprofen carprofen isofezolac
aceloferac fenbufen etodolic acid
fleclozic acid
amfenac efenamic acid
bromfenac ketoprofen fenclofenac
alcofenac orpanoxin zomopirac
diflunisal pranoprofen zaltoprofen

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DETD The present invention is particularly directed to the provision of compositions adapted for treatment of **ophthalmic** tissues. The **ophthalmic** compositions of the present invention will include one or more compounds of formulas (I) and (II) and a pharmaceutically acceptable. . . semi-solid compositions. Suspensions may be preferred for compounds of formulas (I) and (II) which are relatively insoluble in water. The **ophthalmic** compositions of the present invention may also include various other ingredients, such as buffers, preservatives, co-solvents and viscosity building agents.

DETD **Ophthalmic** products are typically packaged in multidose form. Preservatives are thus required to prevent microbial contamination during use. Suitable preservatives include:. . .

DETD . . . the formulations, to decrease physical separation of components of a suspension or emulsion of formulation and/or otherwise to improve the **ophthalmic** formulation. Such viscosity building agents include, for example, polyvinyl alcohol, polyvinyl pyrrolidone, methyl cellulose, hydroxypropyl methylcellulose, hydroxyethyl cellulose, carboxymethyl cellulose,. . .

DETD As indicated above, use of the compounds of formulas (I) and (II) to prevent or reduce damage to **ophthalmic** tissues at the cellular level is a particularly important aspect of the present invention. **Ophthalmic** conditions which may be treated include, but are not limited to, cataracts, retinopathies, heredodegenerative diseases, macular degeneration, ocular ischemia, glaucoma, and damage associated with injuries to **ophthalmic** tissues, such as ischemia reperfusion injuries, photochemical injuries, and injuries associated with ocular surgery, particularly injuries to the retina, cornea. . . other tissues caused by exposure to light or surgical instruments. The compounds may also be used as an adjunct to **ophthalmic** surgery, such as by vitreal or subconjunctival injection following **ophthalmic** surgery. The compounds may be used for acute treatment of temporary conditions, or may be administered chronically, especially in the case of degenerative disease. The compounds may also be used prophylactically, especially prior to ocular surgery or noninvasive **ophthalmic** procedures, or other types of surgery.

DETD Topical **ophthalmic** compositions useful for treating inflammation and/or tissue oxidative damage:

DETD

Component	% w/v
Compound	0.05-5.0
Tyloxapol	0.01-0.05
HPMC	0.5
Benzalkonium Chloride	0.01
Sodium Chloride	0.8
Edetate Disodium	0.01
NaOH/HCl	q.s. pH 7.4
Purified Water	q.s. 100 mL

DETD A preferred topical **ophthalmic** composition useful for treating inflammation and/or tissue oxidative damage:

DETD

Component	% w/v

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Compound E	0.10
Tyloxapol	0.01-0.05
HPMC	0.5
Benzalkonium Chloride	0.01
Sodium Chloride	0.8
Edetate Disodium	0.01
NaOH/HCl	q.s. pH 7.4
Purified Water	q.s. 100 mL

DETD . . . either dry heat or filtered. The sterilized anti-inflammatory agent is weighed aseptically and placed into a pressurized ballmill container. The **tyloxapol**, in sterilized aqueous solution form, is then added to the ballmill container. Sterilized glass balls are then added to the. . .

CLM What is claimed is:

. . . acid; indoprofen; pirprofen; clidanac; fenoprofen; naproxen; fenclorac; meclofenamate; benoxaprofen; carprofen; isofezolac; aceloferac; fenbufen; etodolic acid; fleclozic acid; amfenac; efenamic acid; **bromfenac**; ketoprofen; fenclofenac; alcofenac; orpanoxin; zomopirac; diflunisal; flufenamic acid; niflumic acid; mefenamic acid; pranoprofen; zaltoprofen; indomethacin; sulindac; tolmetin; suprofen; ketorolac; flurbiprofen;. . .

CLM What is claimed is:

. . . acid; indoprofen; pirprofen, clidanac; fenoprofen; naproxen; fenclorac; meclofenamate; benoxaprofen; carprofen; isofezolac; aceloferac; fenbufen; etodolic acid; fleclozic acid; amfenac; efenamic acid; **bromfenac**; ketoprofen; fenclofenac; alcofenac; orpanoxin; zomopirac; diflunisal; flufenamic acid; niflumic acid; mefenamic acid; pranoprofen; zaltoprofen; indomethacin; sulindac; tolmetin; suprofen; ketorolac; flurbiprofen;. . .

CLM What is claimed is:

24. The method according to claim 23, wherein the composition is administered to prevent or alleviate damage to **ophthalmic** tissues.

CLM What is claimed is:

. . . acid; indoprofen; pirprofen; clidanac; fenoprofen; naproxen; fenclorac; meclofenamate; benoxaprofen; carprofen; isofezolac; aceloferac; fenbufen; etodolic acid: fleclozic acid; amfenac; efenamic acid; **bromfenac**; ketoprofen; fenclofenac; alcofenac; orpanoxin; zomopirac; diflunisal; flufenamic acid; niflumic acid; mefenamic acid; pranoprofen; zaltoprofen; indomethacin; sulindac; tolmetin; suprofen; ketorolac; flurbiprofen;. . .

IT Drug delivery systems
(**ophthalmic**; preparation of esters of non-steroidal antiinflammatory agents with antioxidant activity)

L9 ANSWER 33 OF 38 USPATFULL on STN
ACCESSION NUMBER: 97:68150 USPATFULL
TITLE: Preserved **ophthalmic** drug compositions containing polymeric quaternary ammonium compounds
INVENTOR(S): Desai, Suketu Dipakbhai, Fort Worth, TX, United States

Jagoe

	Nelms, Diane S., Fort Worth, TX, United States
PATENT ASSIGNEE(S):	Alcon Laboratories, Inc., Fort Worth, TX, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5653972		19970805	<--
APPLICATION INFO.:	US 1996-700960		19960821	(8)

RELATED APPLN. INFO.: Division of Ser. No. US 1994-340763, filed on 16 Nov 1994
DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Page, Thurman K.
ASSISTANT EXAMINER: Howard, Sharon
LEGAL REPRESENTATIVE: Ryan, Patrick M.
NUMBER OF CLAIMS: 5
EXEMPLARY CLAIM: 1
LINE COUNT: 309
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

TI Preserved **ophthalmic** drug compositions containing polymeric quaternary ammonium compounds

AB Disclosed are storage-stable preserved **ophthalmic** compositions containing acidic drugs in combination with polymeric quaternary ammonium compounds and boric acid.

SUMM The present invention relates generally to **ophthalmic** compositions. In particular, the present invention relates to the use of a polymeric quaternary ammonium compound and boric acid to provide preserved, storage-stable **ophthalmic** compositions of acidic drugs.

SUMM **Ophthalmic** formulations generally contain one or more active compounds along with excipients such as surfactants, comforting agents, complexing agents, stabilizers, buffering systems, chelating agents, viscosity agents or gelling polymers and anti-oxidants. **Ophthalmic** formulations which are intended for multidose use require a preservative.

SUMM Organo-mercurials have been used as preservatives in **ophthalmic** formulations including **ophthalmic** solutions of acidic drugs. These organo-mercurials include thimerosal, phenylmercuric acetate and phenylmercuric nitrate. Organo-mercurials, however, have limitations due to potential. . .

SUMM Sorbic acid, has also been used to preserve **ophthalmic** formulations, but it too possesses poor chemical stability as well as poor antimicrobial activity.

SUMM Benzalkonium chloride is a widely used preservative in **ophthalmic** solutions. However, benzalkonium chloride and other quaternary ammonium compounds are generally considered to be incompatible with **ophthalmic** compositions of drugs with acidic groups, such as nonsteroidal antiinflammatory drugs ("NSAIDS"). These preservative lose their ability to function as. . .

SUMM U.S. Pat. No. 5,110,493 discloses stable **ophthalmic** NSAID formulations which do not contain organo-mercurial preservatives. Instead, the reference NSAID formulations use quaternary ammonium compounds, such as cetyltrimethylammonium. . .

SUMM PCT application WO 94/15597 discloses the use of lauralkonium chloride, the C.sub.12 homolog of benzalkonium chloride, in **ophthalmic** formulations of drugs which are incompatible with benzalkonium chloride. Unlike the mixture of alkyldimethylbenzylammonium chloride known as benzalkonium chloride, this. . .

SUMM . . . safe, stable, and able to meet both the United States Pharmacopoeia (USP) and European Pharmacopoeia (Ph.Eur.) preservative effectiveness requirements for **ophthalmic** formulations of acidic drugs has forced pharmaceutical companies to develop more than one formulation of the same drug, with each. . .

SUMM U.S. Pat. No. 4,960,799 discloses storage stable aqueous **ophthalmic** compositions containing diclofenac, a nonsteroidal antiinflammatory drug, and/or its pharmaceutically acceptable salts. The reference compositions include EDTA as a stabilizing. . .

SUMM . . . None of these references disclose the use of a polymeric quaternary ammonium compound as a preservative in any formulations of **ophthalmic** drugs.

SUMM . . . discovered that the use of a combination of a polymeric quaternary ammonium compound such as Polyquad® and boric acid in **ophthalmic** compositions of acidic drugs provides a storage-stable composition which has surprisingly good preservative efficacy. This preservative combination of a polymeric quaternary ammonium compound and boric acid is useful in **ophthalmic** compositions of acidic drugs such as prostaglandins, antifungals, antibacterials, and diagnostic agents. This preservative combination is especially useful in **ophthalmic** solutions of drugs containing either a carboxyl group such as non-steroidal antiinflammatory drugs (NSAIDS) or a sulfonamide group such as. . .

SUMM Among other factors, the present invention is based on the discovery that **ophthalmic** compositions containing a polymeric quaternary ammonium compound and boric acid may be effectively preserved by the USP and Ph.Eur. preservative. . .

SUMM Suitable **ophthalmic** agents which may be included in the compositions of the present invention and administered via the method of the present. . . derivatives; non-steroidal anti-inflammatory agents, including but not limited to those classified as aryl- or heteroaryl-alkanoic acids, such as diclofenac, **bromfenac**, flurbiprofen, suprofen, ketorolac, indomethacin and ketoprofen; anti-bacterials and anti-infectives, including sulfa drugs, such as sulfacetamide sodium, and beta-lactams such as penicillins and cephalosporins; and diagnostic agents such as sodium fluorescein. Combinations of **ophthalmic** agents may also be used in the compositions of the present invention.

SUMM . . . chlorobutanol, and biguanides such as chlorhexidine and hydroxypropyl methyl biguanide), surfactants (e.g. poloxamers such as Pluronics®; polysorbates such as Tweens®; **tyloxapol**; sarcosinates such as Hamposyl®; and polyethoxylated castor oils such as Cremophor®), and tonicity agents (e.g., sodium chloride, mannitol, dextrose and. . .

SUMM The **ophthalmic** compositions of the present invention may additionally contain polymers which will undergo sol-to-gel transition upon exposure to physical or chemical. . .

DETD . . . the formulation. The rate or level of antimicrobial activity determined compliance with the USP and/or Ph.Eur. preservative efficacy standards for **ophthalmic** preparations.

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DETD The compendial preservative standards for **ophthalmic** preparations are presented below:

DETD . . . of the preservative challenge study conducted on Formulation A are shown below in Table 1. These results illustrate that an **ophthalmic** formulation of an acidic drug can be globally preserved, that is, can comply with the USP and Ph.Eur. A preservative effectiveness requirements for **ophthalmic** preparations, using a combination of a polymeric quaternary ammonium compound and boric acid.

CLM What is claimed is:

1. A method for treating or controlling ocular inflammation comprising the topical ocular application of a preserved storage stable **ophthalmic** composition comprising a therapeutically-effective amount of one or more acidic non-steroidal anti-inflammatory agents, a combination of an antimicrobial polymeric quaternary. . .

CLM What is claimed is:

5. The method of claim 2 wherein the non-steroidal anti-inflammatory agent is selected from the group consisting of **bromfenac** and its ophthalmically acceptable salts, esters, amides or prodrugs.

ST **ophthalmic** prepn quaternary ammonium polymer preservative; diclofenac borate Polyquad **ophthalmic** prepn

IT Inflammation inhibitors
(nonsteroidal; preserved **ophthalmic** drug compns. containing polymeric quaternary ammonium compds.)

IT Biocides

IT Glaucoma (disease)
(preserved **ophthalmic** drug compns. containing polymeric quaternary ammonium compds.)

IT Diagnosis
(agents, preserved **ophthalmic** drug compns. containing polymeric quaternary ammonium compds.)

IT Pharmaceutical dosage forms
(**ophthalmic**, preserved **ophthalmic** drug compns. containing polymeric quaternary ammonium compds.)

IT Quaternary ammonium compounds, biological studies
(polymers, preserved **ophthalmic** drug compns. containing polymeric quaternary ammonium compds.)

IT 53-86-1, Indomethacin 5104-49-4, Flurbiprofen 10043-35-3, Boric acid, biological studies 10043-35-3D, Boric acid, polyol complexes 15307-79-6, Sodium diclofenac 15307-86-5, Diclofenac 22071-15-4, Ketoprofen 40828-46-4, Suprofen 74103-06-3, Ketorolac 75345-27-6, Polyquaternium-1 91714-94-2, **Bromfenac**
(preserved **ophthalmic** drug compns. containing polymeric quaternary ammonium compds.)

L9 ANSWER 34 OF 38 USPATFULL on STN

ACCESSION NUMBER: 97:14409 USPATFULL

TITLE: Preserved **ophthalmic** drug compositions containing polymeric quaternary ammonium compounds

INVENTOR(S): Desai, Suketu D., Fort Worth, TX, United States
Nelms, Diane S., Fort Worth, TX, United States

PATENT ASSIGNEE(S): Alcon Laboratories, Inc., Fort Worth, TX, United States (U.S. corporation)

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	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5603929		19970218	<--
APPLICATION INFO.:	US 1994-340763		19941116	(8)

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Page, Thurman K.
ASSISTANT EXAMINER: Howard, Sharon
LEGAL REPRESENTATIVE: Ryan, Patrick M.
NUMBER OF CLAIMS: 20
EXEMPLARY CLAIM: 1
LINE COUNT: 361
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

TI Preserved **ophthalmic** drug compositions containing polymeric quaternary ammonium compounds

AB Disclosed are storage-stable preserved **ophthalmic** compositions containing acidic drugs in combination with polymeric quaternary ammonium compounds and boric acid.

SUMM The present invention relates generally to **ophthalmic** compositions. In particular, the present invention relates to the use of a polymeric quaternary ammonium compound and boric acid to provide preserved, storage-stable **ophthalmic** compositions of acidic drugs.

SUMM **Ophthalmic** formulations generally contain one or more active compounds along with excipients such as surfactants, comforting agents, complexing agents, stabilizers, buffering systems, chelating agents, viscosity agents or gelling polymers and anti-oxidants. **Ophthalmic** formulations which are intended for multidose use require a preservative.

SUMM Organo-mercurials have been used as preservatives in **ophthalmic** formulations including **ophthalmic** solutions of acidic drugs. These organo-mercurials include thimerosal, phenylmercuric acetate and phenylmercuric nitrate. Organo-mercurials, however, have limitations due to potential. . .

SUMM Sorbic acid, has also been used to preserve **ophthalmic** formulations, but it too possesses poor chemical stability as well as poor antimicrobial activity.

SUMM Benzalkonium chloride is a widely used preservative in **ophthalmic** solutions. However, benzalkonium chloride and other quaternary ammonium compounds are generally considered to be incompatible with **ophthalmic** compositions of drugs with acidic groups, such as nonsteroidal antiinflammatory drugs ("NSAIDS"). These preservative lose their ability to function as. . .

SUMM U.S. Pat. No. 5,110,493 discloses stable **ophthalmic** NSAID formulations which do not contain organo-mercurial preservatives. Instead, the reference NSAID formulations use quaternary ammonium compounds, such as cetyltrimethylammonium. . .

SUMM PCT application WO 94/15597 discloses the use of lauralkonium chloride, the C.sub.12 homolog of benzalkonium chloride, in **ophthalmic** formulations of drugs which are incompatible with benzalkonium chloride. Unlike the mixture of alkyldimethylbenzylammonium chloride known as benzalkonium chloride, this. . .

SUMM . . . stable, and able to meet both the United States Pharmacopoeia (USP) and European Pharmacopoeia (Ph. Eur.) preservative effectiveness requirements for **ophthalmic** formulations of acidic drugs has forced pharmaceutical companies to develop more than one formulation of the same drug, with each. . .

SUMM U.S. Pat. No. 4,960,799 discloses storage stable aqueous **ophthalmic** compositions containing diclofenac, a nonsteroidal antiinflammatory drug, and/or its pharmaceutically acceptable salts. The reference compositions include EDTA as a stabilizing. . .

SUMM . . . contact lens and artificial tear solutions, also discloses the use of certain polymeric quaternary ammonium compounds in formulations containing certain **ophthalmic** drugs. However, neither this reference nor any of the other references mentioned above discloses the use of a polymeric quaternary ammonium compound as a preservative in formulations of acidic **ophthalmic** drugs, that is, drugs which may be incompatible with positively charged preservatives.

SUMM . . . discovered that the use of a combination of a polymeric quaternary ammonium compound such as POLYQUAD® and boric acid in **ophthalmic** compositions of acidic drugs provides a storage-stable composition which has surprisingly good preservative efficacy. This preservative combination of a polymeric quaternary ammonium compound and boric acid is useful in **ophthalmic** compositions of acidic drugs such as prostaglandins, antifungals, antibactedals, and diagnostic agents. This preservative combination is especially useful in **ophthalmic** solutions of drugs containing either a carboxyl group such as non-steroidal anti-inflammatory drugs (NSAIDS) or a sulfonamide group such as. . .

SUMM Among other factors, the present invention is based on the discovery that **ophthalmic** compositions containing a polymeric quaternary ammonium compound and boric acid may be effectively preserved by the USP and Ph. Eur.. . .

DETD Suitable **ophthalmic** agents which may be included in the compositions of the present invention and administered via the method of the present. . . derivatives; non-steroidal anti-inflammatory agents, including but not limited to those classified as aryl- or heteroaryl-alkanoic acids, such as diclofenac, **bromfenac**, flurbiprofen, suprofen, ketorolac, indomethacin and ketoprofen; anti-bacterials and anti-infectives, including sulfa drugs, such as sulfacetamide sodium, and beta-lactams such as penicillins and cephalosporins; and diagnostic agents such as sodium fluorescein. Combinations of **ophthalmic** agents may also be used in the compositions of the present invention.

DETD . . . chlorobutanol, and biguanides such as chlorhexidine and hydroxypropyl methyl biguanide), surfactants (e.g. poloxamers such as Pluronics®; polysorbates such as Tweens®; **tyloxapol**; sarcosinates such as Hamposyl®; and polyethoxylated castor oils such as Cremophor®), and tonicity agents (e.g., sodium chloride, mannitol, dextrose and. . .

DETD The **ophthalmic** compositions of the present invention may additionally contain polymers which will undergo sol-to-gel transition upon exposure to physical or chemical. . .

DETD . . . formulation. The rate or level of antimicrobial activity determined compliance with the USP and/or Ph. Eur. preservative efficacy standards for **ophthalmic** preparations.

DETD The compendial preservative standards for **ophthalmic**

preparations are presented below:

DETD . . . of the preservative challenge study conducted on Formulation A are shown below in Table 1. These results illustrate that an **ophthalmic** formulation of an acidic drug can be globally preserved, that is, can comply with the USP and Ph. Eur. A preservative effectiveness requirements for **ophthalmic** preparations, using a combination of a polymeric quaternary ammonium compound and boric acid.

CLM What is claimed is:
1. A storage stable **ophthalmic** composition comprising a therapeutically effective amount of one or more acidic **ophthalmic** agents, a combination of an antimicrobial polymeric quaternary ammonium compound and boric acid in an amount effective to meet at. . . minimum United States Pharmacopeia XXII and European Pharmacopeia (1994) preservative effectiveness requirements, and an ophthalmically acceptable vehicle; wherein the acidic **ophthalmic** agent is selected from the group consisting of anti-glaucoma and non-steroidal anti-inflammatory agents; provided that the composition does not contain. . .

CLM What is claimed is:
2. The composition of claim 1 wherein the **ophthalmic** agent is a non-steroidal anti-inflammatory agent.

CLM What is claimed is:
. . . The composition of claim 3 wherein the non-steroidal anti-inflammatory agent is selected from the group consisting of: diclofenac, flurbiprofen, suprofen, **bromfenac**, keterolac, indomethacin, ketaprofen, and ophthalmically acceptable salts, esters, amides or prodrugs thereof.

CLM What is claimed is:
7. The composition of claim 4 wherein the non-steroidal anti-inflammatory agent is selected from the group consisting of **bromfenac** and its ophthalmically acceptable salts, esters, amides, or prodrugs thereof.

CLM What is claimed is:
19. An **ophthalmic** formulation comprising diclofenac or an ophthalmically acceptable salt, ester, amide or prodrug thereof, and a combination of an antimicrobial polymeric. . .

ST **ophthalmic** prepn quaternary ammonium polymer preservative; diclofenac borate Polyquad **ophthalmic** prepn

IT Inflammation inhibitors
(nonsteroidal; preserved **ophthalmic** drug compns. containing polymeric quaternary ammonium compds.)

IT Biocides

IT Glaucoma (disease)
(preserved **ophthalmic** drug compns. containing polymeric quaternary ammonium compds.)

IT Diagnosis
(agents, preserved **ophthalmic** drug compns. containing polymeric quaternary ammonium compds.)

IT Pharmaceutical dosage forms
(**ophthalmic**, preserved **ophthalmic** drug compns.

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containing polymeric quaternary ammonium compds.)
IT Quaternary ammonium compounds, biological studies
(polymers, preserved **ophthalmic** drug compns. containing polymeric quaternary ammonium compds.)
IT 53-86-1, Indomethacin 5104-49-4, Flurbiprofen 10043-35-3, Boric acid, biological studies 10043-35-3D, Boric acid, polyol complexes 15307-79-6, Sodium diclofenac 15307-86-5, Diclofenac 22071-15-4, Ketoprofen 40828-46-4, Suprofen 74103-06-3, Ketorolac 75345-27-6, Polyquaternium-1 91714-94-2, **Bromfenac**
(preserved **ophthalmic** drug compns. containing polymeric quaternary ammonium compds.)

L9 ANSWER 35 OF 38 USPAT2 on STN
ACCESSION NUMBER: 2004:334304 USPAT2
TITLE: Cyclooxygenase-2 inhibitor compositions having rapid onset of therapeutic effect
INVENTOR(S): Kararli, Tugrul T., Skokie, IL, UNITED STATES
Kontny, Mark J., Libertyville, IL, UNITED STATES
Desai, Subhash, Wilmette, IL, UNITED STATES
Hageman, Michael J., Portage, MI, UNITED STATES
Haskell, Royal J., Kalamazoo, MI, UNITED STATES(4)
PATENT ASSIGNEE(S): Pharmacia Corporation, St. Louis, MO, UNITED STATES (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 7172769	B2	20070206	
	WO 2001041760		20010614	<--
APPLICATION INFO.:	US 2000-31898		20001206	(10)
	WO 2000-US32434		20001206	
			20020730	PCT 371 date

	NUMBER	DATE
PRIORITY INFORMATION:	US 1999-169856P	19991209 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: GRANTED
PRIMARY EXAMINER: Azpuru, Carlos A.
LEGAL REPRESENTATIVE: Fitzsimmons, Patricia K., Ashbrook, Charles
NUMBER OF CLAIMS: 17
EXEMPLARY CLAIM: 1,2
NUMBER OF DRAWINGS: 4 Drawing Figure(s); 3 Drawing Page(s)
LINE COUNT: 1893
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

DETD . . . conditions such as psoriasis, eczema, acne, burns, dermatitis and ultraviolet radiation damage including sunburn, and post-operative inflammation including that following **ophthalmic** surgery such as cataract surgery or refractive surgery.
DETD Such compositions are useful in treatment of **ophthalmic** diseases, such as retinitis, conjunctivitis, retinopathies, uveitis, ocular photophobia, and of acute injury to the eye tissue.
DETD . . . ammonium salicylate, ampiroxicam, amtolmetin guacil, anileridine, antipyrine, antipyrine salicylate, antrafenine, apazone,

bendazac, benorylate, benoxaprofen, benzpiperylon, benzydamine, benzylmorphine, bermoprofen, bezitrarnide, α-bisabolol, **bromfenac**, ρ-bromoacetanilide, 5-bromosalicylic acid acetate, bromosaligenin, bucetin, bucloxic acid, bucolome, bufexamac, bumadizon, buprenorphine, butacetin, butibufen, butophanol, calcium acetylsalicylate, carbamazepine, carbiphene, carprofen,. . .

DETD . . . In this embodiment the surface modifying agent is a nonionic liquid polymer of the alkylaryl polyether alcohol type, for example **tyloxapol**. Optionally an additional surface modifying agent can be present.

DETD . . . of an oil, a selective COX-2 inhibitory drug in the presence of surface modifying agents (e.g., gelatin, casein, lecithin, polyvinylpyrrolidone, **tyloxapol**, poloxamers, other block polymers, etc.) substantially as disclosed in above-cited U.S. Pat. No. 5,560,931. In this embodiment, the drug particles. . .

DETD . . . comprising a first particle distribution of a selective COX-2 inhibitory drug together with a surface modifying agent such as polysulfated **tyloxapol** by a process comprising the steps of (a) placing the dispersion between a first electrode and a second electrode; and. . .

DETD . . . fatty acid esters, for example glyceryl monostearate, sorbitan esters, for example sorbitan monolaurate, sorbitan monooleate, sorbitan monopalmitate and sorbitan monostearate, **tyloxapol**, and mixtures thereof. Such wetting agents, if present, constitute in total about 0.25% to about 15%, preferably about 0.4% to. . .

L9 ANSWER 36 OF 38 USPAT2 on STN

ACCESSION NUMBER:	2004:307964 USPAT2			
TITLE:	Dual-release compositions of a cyclooxygenase-2 inhibitor			
INVENTOR(S):	Desai, Subhash, Wilmette, IL, UNITED STATES Nadkarni, Sreekant R., Gurnee, IL, UNITED STATES Wald, Randy J., Portage, MI, UNITED STATES DeBrincat, Gary A., Battle Creek, MI, UNITED STATES			
PATENT ASSIGNEE(S):	Pharmacia Corporation (of Pfizer, Inc.), St Louis, MO, UNITED STATES (U.S. corporation)			
	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 7220434	B2	20070522	
	WO 2001045706		20010628	<--
APPLICATION INFO.:	US 2000-169039		20001220	(10)
	WO 2000-US34754		20001220	
			20040223	PCT 371 date
DOCUMENT TYPE:	Utility			
FILE SEGMENT:	GRANTED			
PRIMARY EXAMINER:	Hartley, Michael G.			
ASSISTANT EXAMINER:	Ebrahim, Nabila			
LEGAL REPRESENTATIVE:	Fitzsimmons, Patricia K., Ashbrook, Charles W.			
NUMBER OF CLAIMS:	18			
EXEMPLARY CLAIM:	1			
NUMBER OF DRAWINGS:	1 Drawing Figure(s); 1 Drawing Page(s)			
LINE COUNT:	2151			

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

DETD . . . conditions such as psoriasis, eczema, acne, burns, dermatitis and ultraviolet radiation damage including sunburn, and post-operative inflammation including that following **ophthalmic** surgery such as cataract surgery or refractive surgery.

DETD Such compositions are useful in treatment of **ophthalmic** diseases, such as retinitis, conjunctivitis, retinopathies, uveitis, ocular photophobia, and of acute injury to the eye tissue.

DETD . . . ammonium salicylate, ampiroxicam, amtolmetin guacil, anileridine, antipyrine, antipyrine salicylate, antrafenine, apazone, bendazac, benorylate, benoxaprofen, benzpiperylon, benzydamine, benzylmorphine, bermoprofen, bezitramide, α-bisabolol, **bromfenac**, p-bromoacetanilide, 5-bromosalicylic acid acetate, bromosaligenin, bucetin, bucloxic acid, bucolome, bufexamac, bumadizon, buprenorphine, butacetin, butibufen, butophanol, calcium acetylsalicylate, carbamazepine, carbiphene, carprofen,. . .

DETD . . . fatty acid esters, for example glyceryl monostearate, sorbitan esters, for example sorbitan monolaurate, sorbitan monooleate, sorbitan monopalmitate and sorbitan monostearate, **tyloxapol**, and mixtures thereof. Such wetting agents, if present, constitute in total about 0.25% to about 15%, preferably about 0.4% to. . .

L9 ANSWER 37 OF 38 USPAT2 on STN

ACCESSION NUMBER:	2002:48624 USPAT2
TITLE:	Compositions and methods for treating **ophthalmic** and otic infections
INVENTOR(S):	Cagle, Gerald, Fort Worth, TX, United States Abshire, Robert L., Fort Worth, TX, United States Stroman, David W., Irving, TX, United States McLean, Celeste H., Fort Worth, TX, United States Clark, Linda L., Grandview, TX, United States Yanni, John M., Burleson, TX, United States
PATENT ASSIGNEE(S):	Alcon Manufacturing, Ltd., Fort Worth, TX, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 6440964	B2	20020827	<--
APPLICATION INFO.:	US 2001-887771		20010622 (9)	
RELATED APPLN. INFO.:	Continuation-in-part of Ser. No. US 577262			

	NUMBER	DATE
PRIORITY INFORMATION:	US 1998-102504P	19980930 (60)
	US 1998-102506P	19980930 (60)

DOCUMENT TYPE:	Utility
FILE SEGMENT:	GRANTED
PRIMARY EXAMINER:	Fay, Zohreh
LEGAL REPRESENTATIVE:	Brown, Gregg C.
NUMBER OF CLAIMS:	6
EXEMPLARY CLAIM:	1
NUMBER OF DRAWINGS:	1 Drawing Figure(s); 1 Drawing Page(s)
LINE COUNT:	510

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

Jagoe

TI Compositions and methods for treating **ophthalmic** and otic infections

AB **Ophthalmic**, otic and nasal compositions containing a new class of antibiotics (e.g., moxifloxacin) are disclosed. The compositions preferably also contain one or more anti-inflammatory agents. The compositions may be utilized to treat **ophthalmic**, otic and nasal conditions by topically applying the compositions to the affected tissues. The compositions and methods of the invention are particularly useful in the treatment of acute otitis externa infections and **ophthalmic** infections attributable to one or both of two newly identified Microbacterium species, Microbacterium otitidis and Microbacterium alconae.

SUMM The present invention is directed to the provision of topical antibiotic pharmaceutical compositions for the treatment of **ophthalmic**, otic and nasal infections, particularly bacterial infections, and to methods of treating **ophthalmic**, otic and nasal infections by applying those compositions to the affected tissues. The compositions and methods of the invention are. . .

SUMM Quinolone antibiotics have been previously utilized to treat **ophthalmic** and otic infections. For example, a topical **ophthalmic** composition containing the quinolone ciprofloxacin is marketed by Alcon Laboratories, Inc. under the name CILOXAN.TM. (Ciprofloxacin 0.3%) **Ophthalmic** Solution, and a topical otic composition containing a combination of ciprofloxacin and hydrocortisone is marketed by Alcon Laboratories, Inc. under the name CIPRO.TM. HC. The following quinolones have also been utilized in **ophthalmic** antibiotic compositions:

SUMM The foregoing quinolone antibiotic compositions are generally effective in treating **ophthalmic** infections, and have distinct advantages over prior **ophthalmic** antibiotic compositions, particularly those having relatively limited spectrums of antimicrobial activity, such as: neomycin, polymyxin B, gentamicin and tobramycin, which. . . and bacitracin, gramicidin, and erythromycin, which are primarily active against gram positive pathogens. However, despite the general efficacy of the **ophthalmic** quinolone therapies currently available, there is a need for improved compositions and methods of treatment based on the use of antibiotics that are more effective than existing antibiotics against key **ophthalmic** pathogens, and less prone to the development of resistance by those pathogens.

SUMM **Ophthalmic**, otic and nasal infections are frequently accompanied by inflammation of the infected **ophthalmic**, otic and nasal tissues and perhaps even surrounding tissues. Similarly, **ophthalmic**, otic and nasal surgical procedures that create a risk of microbial infections frequently also cause inflammation of the affected tissues. Thus, there is also a need for **ophthalmic**, otic and nasal pharmaceutical compositions that combine the anti-infective activity of one or more antibiotics with the anti-inflammatory activity of. . .

SUMM The invention is based on the use of a potent new class of antibiotics to treat **ophthalmic**, otic and nasal infections, as well as the use of these antibiotics prior to surgery to sterilize the surgical field and prophylactically following surgery or other trauma to

ophthalmic, otic or nasal tissues to minimize the risk of infection. The compositions of the present invention may also be administered to the affected tissues during **ophthalmic**, otic or nasal surgical procedures to prevent or alleviate post-surgical infection. As utilized herein, the terms "treat", "treating" and derivations. . .

SUMM The compositions preferably also contain one or more anti-inflammatory agents to treat inflammation associated with infections of **ophthalmic**, otic or nasal tissues. The anti-inflammatory component of the compositions is also useful in treating inflammation associated with physical trauma to **ophthalmic**, otic or nasal tissues, including inflammation resulting from surgical procedures. The compositions of the present invention are therefore particularly useful in treating inflammation associated with trauma to **ophthalmic**, otic or nasal tissues wherein there is either an infection or a risk of an infection resulting from the trauma.

SUMM Examples of **ophthalmic** conditions that may be treated with the compositions of the present invention include conjunctivitis, keratitis, blepharitis, dacyrocystitis, hordeolum and corneal ulcers. The compositions of the invention may also be used prophylactically in connection with various **ophthalmic** surgical procedures that create a risk of infection.

SUMM . . . that have been identified as being associated with acute otitis extema infections have also been discovered to be associated with **ophthalmic** infections. As indicated above, the antibiotics utilized in the present invention have a high level of antimicrobial activity against these newly discovered **ophthalmic** pathogens, and as a result, the compositions of the present invention are particularly useful in treating **ophthalmic** infections involving these species.

SUMM The compositions of the present invention are specially formulated for topical application to **ophthalmic**, otic and nasal tissues. The compositions are preferably sterile, and have physical properties (e.g., osmolality and pH) that are specially suited for application to **ophthalmic**, otic and nasal tissues, including tissues that have been compromised as the result of preexisting disease, trauma, surgery or other. . .

DETD . . . to as the "minimum bactericidal concentration" or "MBC". The minimum inhibitory concentration of Moxifloxacin for several bacteria commonly associated with **ophthalmic**, otic and nasal infections are provided in the following table:

DETD Microbacterium otitidis and Microbacterium alconae have also been discovered to be pathogens in infections of **ophthalmic** tissues, such as conjunctivitis and blepharitis. The compositions of the present invention are therefore particularly useful in treating **ophthalmic** infections involving one or both of these species.

DETD The appropriate antibiotic concentration for **ophthalmic** compositions will generally be an amount of one or more antibiotics of formula (I) sufficient to provide a concentration in. . . to or greater than the MIC.sub.90 level for the selected antibiotic(s), relative to gram-negative and gram-positive organisms commonly associated with **ophthalmic** infections. The appropriate concentration for otic and nasal compositions will generally be an amount of one or more antibiotics of. . .

DETD The preferred glucocorticoids for **ophthalmic** and otic use include dexamethasone, loteprednol, rimexolone, prednisolone, fluorometholone, and hydrocortisone. The preferred glucocorticoids for nasal use include mometasone, fluticasone,. . .

DETD . . . described in U.S. Pat. No. 5,223,493 (Boltralik) are also preferred steroidal anti-inflammatory agents, particularly with respect to compositions for treating **ophthalmic** inflammation. The following compounds are especially preferred: ##STR4##

DETD . . . to as cyclooxygenase type I and type II inhibitors, such as diclofenac, flurbiprofen, ketorolac, suprofen, nepafenac, amfenac, indomethacin, naproxen, ibuprofen, **bromfenac**, ketoprofen, meclofenamate, piroxicam, sulindac, mefanamic acid, diflusinal, oxaprozin, tolmetin, fenoprofen, benoxaprofen, nabumetome, etodolac, phenylbutazone, aspirin, oxyphenbutazone, NCX-4016, HCT-1026, NCX-284, NCX-456,. . .

DETD . . . agents selected and the type of inflammation being treated. The concentrations will be sufficient to reduce inflammation in the targeted **ophthalmic**, otic or nasal tissues following topical application of the compositions to those tissues. Such an amount is referred to herein. . .

DETD The compositions are typically administered to the affected **ophthalmic**, otic or nasal tissues by topically applying one to four drops of a sterile solution or suspension, or a comparable. . . four times per day. However, the compositions may also be formulated as irrigating solutions that are applied to the affected **ophthalmic**, otic or nasal tissues during surgical procedures.

DETD The **ophthalmic**, otic and nasal compositions of the present invention will contain one or more compounds of formula (I) and preferably one. . . agents, in pharmaceutically acceptable vehicles. The compositions will typically have a pH in the range of 4.5 to 8.0. The **ophthalmic** compositions must also be formulated to have osmotic values that are compatible with the aqueous humor of the eye and **ophthalmic** tissues. Such osmotic values will generally be in the range of from about 200 to about 400 milliosmoles per kilogram. . .

DETD **Ophthalmic**, otic and nasal pharmaceutical products are typically packaged in multidose form. Preservatives are thus required to prevent microbial contamination during. . .

DETD The following examples are provided to further illustrate the **ophthalmic**, otic and nasal compositions of the present invention.

DETD

Ophthalmic/Otic/Nasal Solution

Ingredient	Amount (wt. %)
Moxifloxacin	0.35
Sodium Acetate	0.03
Acetic Acid	0.04
Mannitol	4.60
EDTA	0.05
Benzalkonium Chloride. . .	

DETD

Ophthalmic/Otic/Nasal Suspension

Ingredient Amount (wt. %)

Moxifloxacin 0.3
Dexamethasone, Micronized USP 0.10
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 q.s. for pH adjustment to 5.5
Sodium Hydroxide, NF
Purified Water, USP q.s. to 100
DETD

Ophthalmic Ointment
Ingredient Amount (wt. %)

Moxifloxacin 0.35
Mineral Oil, USP 2.0
White petrolatium, USP q.s 100
DETD

Ophthalmic Ointment
Ingredient Amount (wt. %)

Moxifloxacin 0.3
Fluorometholone Acetate, USP 0.1
Chlorobutanol, Anhydrous, NF 0.5
Mineral Oil, USP 5
. . .
CLM What is claimed is:
1. A topical pharmaceutical composition for treating acute otitis externa infections or **ophthalmic** infections attributable to a Microbacterium species selected from the group consisting of Microbacterium otitidis and Microbacterium alconae, comprising of one.
. .
CLM What is claimed is:
6. A method of treating acute otitis externa infections or **ophthalmic** infections attributable to a Microbacterium species selected from the group consisting of Microbacterium otitidis and Microbacterium alconae, which comprises instilling. . .
IT Drug delivery systems
(**ophthalmic**; antibiotic compns. for treatment of eye and ear and nose disorders)

L9 ANSWER 38 OF 38 USPAT2 on STN
ACCESSION NUMBER: 2002:48047 USPAT2
TITLE: Use of a celecoxib composition for fast pain relief
INVENTOR(S): Karim, Aziz, Skokie, IL, United States
Brugger, Andrew M., Libertyville, IL, United States
Gao, Ping, Portage, MI, United States
Hassan, Fred, Peapack, NJ, United States
Forbes, James C., Glenview, IL, United States

Jagoe

PATENT ASSIGNEE(S): Pharmacia Corporation, St. Louis, MO, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 6579895	B2	20030617	<--
APPLICATION INFO.:	US 2001-866165		20010525 (9)	

	NUMBER	DATE
PRIORITY INFORMATION:	US 2000-207729P	20000526 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: GRANTED
PRIMARY EXAMINER: Cook, Rebecca
LEGAL REPRESENTATIVE: Harness, Dickey & Pierce
NUMBER OF CLAIMS: 29
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 4 Drawing Figure(s); 4 Drawing Page(s)
LINE COUNT: 1140
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

DETD . . . of ICI), propylene glycol laurate (e.g., Lauroglycol.TM. of Gattefosse), sodium lauryl sulfate, sorbitan monolaurate, sorbitan monooleate, sorbitan monopalmitate, sorbitan monostearate, **tyloxapol**, and mixtures thereof. Presently preferred examples include polysorbate 80 and sodium lauryl sulfate.

DETD . . . conditions such as psoriasis, eczema, acne, bums, dermatitis and ultraviolet radiation damage including sunburn, and post-operative inflammation including that following **ophthalmic** surgery such as cataract surgery or refractive surgery.

DETD Such compositions are useful in treatment of **ophthalmic** diseases, such as retinitis, conjunctivitis, retinopathies, uveitis, ocular photophobia, and of acute injury to the eye tissue.

DETD . . . ammonium salicylate, ampiroxicam, amtolmetin guacil, anileridine, antipyrine, antipyrine salicylate, antrafenine, apazone, bendazac, benorylate, benoxaprofen, benzpiperylon, benzydamine, benzylmorphine, bermoprofen, bezitramide, α-bisabolol, **bromfenac**, p-bromoacetanilide, 5-bromosalicylic acid acetate, bromosaligenin, bucetin, bucloxic acid, bucolome, bufexamac, bumadizon, buprenorphine, butacetin, butibufen, butophanol, calcium acetylsalicylate, carbamazepine, carbiphene, carprofen,. . .

=> FIL STNGUIDE

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	136.82	147.72

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	-1.70	-1.70

FILE 'STNGUIDE' ENTERED AT 16:28:53 ON 14 JUN 2010
USE IS SUBJECT TO THE TERMS OF YOUR CUSTOMER AGREEMENT

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10/525006

FILE CONTAINS CURRENT INFORMATION.
LAST RELOADED: Jun 11, 2010 (20100611/UP).

=>

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WEST Search History for Application 10525006

Creation Date: 2010061516:29

bromfecanPGPB, USPT, USOC, EPAB, JPAB, DWPI ADJ YES 05-30-2009
bromfenacPGPB, USPT, USOC, EPAB, JPAB, DWPI ADJ YES 05-30-2009
tyloxapolPGPB, USPT, USOC, EPAB, JPAB, DWPI ADJ YES 05-30-2009
sterilePGPB, USPT, USOC, EPAB, JPAB, DWPI ADJ YES 05-30-2009
isotonicPGPB, USPT, USOC, EPAB, JPAB, DWPI ADJ YES 05-30-2009
pHPGPB, 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

Prior Art Searches

Query	DB	Op.	Plur.	Thes.	Date
bromfecan	PGPB, USPT, USOC, EPAB, JPAB, DWPI	ADJ	YES		12-17-2009
bromfenac	PGPB, USPT, USOC, EPAB, JPAB, DWPI	ADJ	YES		12-17-2009
tyloxapol	PGPB, USPT, USOC, EPAB, JPAB, DWPI	ADJ	YES		12-17-2009
sterile	PGPB, USPT, USOC, EPAB, JPAB, DWPI	ADJ	YES		12-17-2009
isotonic	PGPB, USPT, USOC, EPAB, JPAB, DWPI	ADJ	YES		12-17-2009
pH	PGPB, USPT, USOC, EPAB, JPAB, DWPI	ADJ	YES		12-17-2009
(bromfenac) and (tyloxapol) and (sterile) and (isotonic) and (pH)	PGPB, USPT, USOC, EPAB, JPAB, DWPI	ADJ	YES		12-17-2009
5603929.pn.	PGPB, USPT, USOC, EPAB, JPAB, DWPI	ADJ	YES		06-15-2010
5475034.pn.	PGPB, USPT, USOC, EPAB, JPAB, DWPI	ADJ	YES		06-15-2010

((bromfenac) and (tyloxapol) and (sterile) and (isotonic) and (pH))	PGPB, USPT, USOC, EPAB, JPAB, DWPI	ADJ	YES		06-15-2010
2$1amino$7bromobenzoyl$1phenylacetic acid	PGPB, USPT, USOC, EPAB, JPAB, DWPI	ADJ	YES		06-15-2010
$2amino$6bromobenzoyl$1phenylacetic acid	PGPB, USPT, USOC, EPAB, JPAB, DWPI	ADJ	YES		06-15-2010
$2amino$6bromobenzoyl$1benzylacetic acid	PGPB, USPT, USOC, EPAB, JPAB, DWPI	ADJ	YES		06-15-2010
2 amino 3 4 bromo benzoyl phenylacetic acid	PGPB, USPT, USOC, EPAB, JPAB, DWPI	ADJ	YES		06-15-2010

Sheet 1 of 1

INFORMATION DISCLOSURE STATEMENT

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

U.S. DEPARTMENT OF COMMERCE
PATENT AND TRADEMARK OFFICE

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

Date Submitted to PTO: April 8, 2010

ATTY DOCKET NO. 2005_0232A	**SERIAL NO.** 10/525,006
APPLICANT Shirou SAWA et al.	
FILING DATE March 28, 2005	**GROUP** 1614

U.S. PATENT DOCUMENTS

*EXAMINER INITIAL		DOCUMENT NUMBER	DATE	NAME	CLASS	SUBCLASS	FILING DATE IF APPROPRIATE
	AA	6,395,746	5/2002	Cagle et al.			
	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	http://medical-dictionary.thefreedictionary.com/prophylactic accessed 12/15/2009.
	CB	
	CC	
	CD	

EXAMINER	DATE CONSIDERED

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

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: AMENDMENT**

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 $180.00 to cover Patent Office fees relating to filing the following attached papers:

Information Disclosure Statement	$180.00

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
April 8, 2010

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

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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: 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 reference listed on attached Form PTO/SB/08 and any additional information identified below in paragraph 3. A legible copy of each reference listed on the Form PTO/SB/08 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.

04/09/2010 HVUONG1 00000000 10525006
01 FC:1806 180.00 OP

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

1b. [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. [X] Consideration of the following list of additional information (including any copending or abandoned U.S. application, prior uses and/or sales, etc.) is requested.

Copending application Serial No. 11/755,662 which is a CIP of the instant application.

4. For each non-English language reference listed on the attached Form PTO/SB/08, 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. 20005-1503
Telephone (202) 721-8200
Facsimile (202) 721-8250
April 8, 2010

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: Amendment**

AMENDMENT

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

Sir:

Responsive to the Official Action dated December 24, 2009, please amend the above-identified application as follows:

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.

Amendments to the Claims

1-40. (Cancelled)

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 formulated for ophthalmic administration.

42. (Currently amended) The aqueous liquid preparation according to claim 41, wherein the ~~alkyl aryl polyether alcohol type polymer~~ second component 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. (Currently amended) The aqueous liquid preparation according to claim ~~42~~41, wherein the first component is ~~pharmacologically acceptable salt of~~ a 2-amino-3-(4-bromobenzoyl)phenylacetic acid ~~is a~~ sodium salt.

44. (Currently amended) The aqueous liquid preparation according to claim ~~43~~41, wherein the second component is tyloxapol and the pharmacologically acceptable salt of 2-amino-3-(4-bromobenzoyl)phenylacetic acid is a sodium salt , wherein the concentration of the tyloxapol is from about 0.01 w/v % to about 0.5 w/v %; and

wherein the first component is a 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt, wherein the concentration of the 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt is from about 0.01 to about 0.5 w/v %

~~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. (Currently amended) 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 % and the concentration of the 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt is from about 0.05 to about 0.2 w/v %.

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. (Currently amended) The aqueous liquid preparation according to claim ~~46~~45, wherein the concentration of the tyloxapol is about 0.02 w/v %.

48. (Currently amended) The aqueous liquid preparation according to claim ~~47~~41, 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. (Currently amended) The aqueous liquid preparation according to claim ~~50~~49, 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. (Currently amended) The aqueous liquid preparation according to claim ~~53~~45, 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~~ being 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof, and the second component ~~comprising~~ being tyloxapol or polyethylene glycol monostearate, wherein said liquid preparation is formulated for ophthalmic administration.

62. (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 consisting essentially of ~~at least~~ the following two components, the first component ~~comprising~~ being 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof, and the second component ~~comprising being~~ tyloxapol or polyethylene glycol monostearate, together with a preservative, wherein said liquid preparation is formulated for ophthalmic administration.

63. (Cancelled)

64. (New) An aqueous liquid preparation consisting essentially of:

(a) 2-amino-3-(4- bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof,

(b) tyloxapol,

(c) boric acid,

(d) sodium tetraborate,

(e) EDTA sodium salt,

(f) benzalkonium chloride,

(g) polyvinylpyrrolidone, and

(h) sodium sulfite, and wherein said liquid preparation is formulated for ophthalmic administration.

65. (New) The aqueous liquid preparation of claim 64, wherein (a) is a 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt.

66. (New) The aqueous liquid preparation of claim 65, wherein the concentration of the 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt is from about 0.01 to about 0.5 w/v % and the concentration of the tyloxapol is about 0.02 w/v %.

67. (New) The aqueous liquid preparation of claim 66, wherein the concentration of the 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt is about 0.01 w/v %.

68. (New) The aqueous liquid preparation of claim 66, wherein the concentration of the 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt is about 0.1 w/v %.

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 representatives by Examiner Donna Jagoe during the personal interview held on February 16, 2010. The following is a summary of the items discussed during the interview.

Claims 19-40 have been cancelled without prejudice to the filing of a divisional application thereto.

Claims 41, 61 and 62 have been amended to make minor corrections as discussed during the interview.

Claims 42-45, 47-48, 51 and 54 have been amended in minor respects to reorganize the claimed subject matter and change the dependencies.

Claim 63 is cancelled without prejudice.

New claims 64-68 are added for additional patent protection and are supported in the specification at page 8, lines 19-26; page 12, lines 8-28, Table 1 on page 15; and Table 2 on page 17 of the specification. Note that sodium tetraborate is also known as borax, and EDTA sodium salt is also known as sodium edetate, which latter components are recited in Table 2.

Applicant acknowledges with thanks the Examiner's indication that the 103 rejection of claims 41 et al. are likely to be withdrawn in view of the arguments presented at the interview, which arguments are essentially reiterated hereinbelow.

Turning to the Official Action, claims 19-29, 31-34 and 36-38 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 deemed to be overcome by the cancellation of all rejected claims.

Claims 19-29, 31-34, 36-38, 41-51, 53-56, 58-60 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 pending claims for the reasons explained during the interview.

The Examiner asserts that it would have been obvious to substitute the bifunctional ester compounds of Hellberg et al. having anti-inflammatory and anti-oxidant activity 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 December 24, 2009 at page 4. Applicant respectfully disagrees that bromfenac is equivalent to the Hellberg bifunctional ester compounds having both anti-inflammatory and anti-oxidant activity.

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.

See Hellberg et al. at Column 2, lines 38-40.

Moreover, the compounds of Hellberg et al. are intended to offer advantages not provided by the mere administration of individual agents such as bromfenac. Such intended advantages include a uniform delivery of an active molecule, simplifying issues of drug metabolism, toxicity and delivery, as well as 5-lipooxygenase inhibitory activity not present in the individual agents.

> The use of a single agent having both activities over a combination of two different agents provides uniform delivery of an active molecule, thereby simplifying issues of drug metabolism, toxicity and delivery.

See Hellberg et al. at Column 2, lines 7-10.

> Additionally, the compounds of the present invention exhibit 5-lipoxygenase inhibitory activity not present in the individual compounds.

See Hellberg et al. at Column 2, lines 16-18.

> 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 41-44 (emphasis added).

An additional intended advantage of the Hellberg bifunctional ester compounds is disclosed at Col. 2, lines 46 to 56:

> Another advantage of the present invention is that the anti-inflammatory moiety and the anit-oxidant moiety are linked through an ester bond. Since the carboxylic acid moiety of the NSAIA has been converted to an ester, the resultant molecule is neutrally charged, thus increasing lipohilicity and drug delivery.

Thus, the Hellberg bifunctional ester compounds are intended to increase lipophilicity and drug delivery relative to bromfenac alone.

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 proposed substitution of the Hellberg bifunctional anti-inflammatory, anti-oxidant ester compounds 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" with increased "lipophilicity and drug delivery" and "5-lipoxygenase inhibitory activity not present in the individual compounds." Applicant respectfully submits that 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 bromfenac is not equivalent to the Hellberg bifunctional ester compounds and because the proposed substitution would render the Hellberg et al. invention unsatisfactory for its intended purpose and radically change the principle of operation of Hellberg et al., Applicant respectfully submits 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., Applicant submits that Hellberg et al. explicitly teach away from the use of a compound, such as bromfenac, having only anti-inflammatory activity. Hellberg et al. explicitly exclude the use of a single action 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).

See also U.S. Patent No. 5,886,030, a copy of which is enclosed, which states:

> Stinging and burning sensations, as well as general discomfort, are often associated with the topical ophthalmic application of certain types of ophthalmic agents. It is believed that such ocular discomfort is due to the presence of certain functional groups in these agents. Examples of such agents which product ocular discomfort include, but are not limited to, β-blockers such as betaxolol; prostaglandins and prostaglandin derivatives; muscarinics such as pilocarpine; a-adrenergics such as epinephrine, clonidine and apraclonidine; cholinergics such as carbochol; and nonsteroidal anti-inflammatory drugs ("NSAIDS") such as diclofenac and suprofen.

See U.S. Patent No. 5,886,030 at Column 1, lines 21-32.

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. exclude the use of a single NSAIA's by disclosing that such compounds are 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, Applicant respectfully submits a prima facie case of obviousness cannot be based on the combination of Hellberg et al. and Nolan et al.

In addition, one skilled in the art would not have been motivated along the lines of the claimed invention by Hellberg et al. The claimed invention uses the second component as a cosolvent to assist in stabilizing the bromfenac. The second component of the claimed invention is an alkyl aryl polyether alcohol type polymer or a polyethylene glycol fatty acid ester, preferably tyloxapol.

Hellberg et al., however, fail to list tyloxapol as a cosolvent. See column 9, lines 1-5. Instead, Hellberg et al. use tyloxapol for an entirely different purpose. Whereas bromfenac is relatively soluble, the bifunctional ester compounds of Hellberg et al. are relatively lipophilic and insoluble. According to Example 3 bridging columns 11-12, the tyloxapol is apparently used as a milling diluent to grind the relatively insoluble bifunctional ester compound of Hellberg et al. to improve the solubility of the more lipophilic Hellberg ester compounds. In addition, the tyloxapol apparently helps to prevent the ground bifunctional ester compounds from aggregating into larger particles. Therefore the only apparent reason that tyloxapol is used in the compositions of Examples 2 and 3 of Hellberg et al. is as a grinding and anti-aggregation agent for the relatively lipophilic insoluble bifunctional ester compounds of Hellberg et al. Hence one skilled in the art, reading Hellberg et al., would not have been motivated to use tyloxapol in combination with bromfenac, because bromfenac does not suffer from the problems of lipophilicity and insolubility relative to the bifunctional ester compounds of Hellberg et al.

For the reasons detailed above, Applicant respectfully requests 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.

It is believed that all other grounds of rejection have been overcome in view of the instant response. Accordingly, 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.

Rejoinder and allowance of the withdrawn method claims is also solicited.

Respectfully submitted,

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US005886030A

United States Patent [19]

Maniar

[11] Patent Number: 5,886,030

[45] Date of Patent: Mar. 23, 1999

[54] USE OF VITAMIN E TOCOPHERYL DERIVATIVES IN OPHTHALMIC COMPOSITIONS

[75] Inventor: Manoj L. Maniar, San Diego, Calif.

[73] Assignee: Alcon Laboratories, Inc., Fort Worth, Tex.

[21] Appl. No.: 530,516

[22] Filed: Sep. 19, 1995

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 240,057, May 6, 1994, abandoned.

[51] Int. Cl.[6] A61K 31/355

[52] U.S. Cl. 514/458; 514/912

[58] Field of Search 514/458, 912

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Primary Examiner—Zohreh Fay

Attorney, Agent, or Firm—Patrick M. Ryan

[57] ABSTRACT

Disclosed are ophthalmic compositions containing vitamin E tocopheryl derivatives which are comfortable and non-irritating. In addition, these vitamin E tocopheryl derivatives significantly increase the aqueous solubility of certain poorly soluble ophthalmic agents.

9 Claims, No Drawings

USE OF VITAMIN E TOCOPHERYL DERIVATIVES IN OPHTHALMIC COMPOSITIONS

This application is a continuation-in-part application of application Ser. No. 08/240,057 filed May 6, 1994, now abandoned.

BACKGROUND OF THE INVENTION

The present invention relates generally to ophthalmic compositions. In particular, the present invention relates to the use of certain vitamin E tocopheryl derivatives to provide comfortable, non-irritating ophthalmic compositions. In addition, the present invention relates to the use of these vitamin E tocopheryl derivatives to increase the solubility of poorly soluble ophthalmic agents in aqueous compositions. For purposes of the present specification, the vitamin E tocopheryl derivatives useful in the present invention shall be referred to as "vitamin E tocopheryl derivatives" or "vitamin E derivatives" or "TPGS."

Stinging and burning sensations, as well as general discomfort, are often associated with the topical ophthalmic application of certain types of ophthalmic agents. It is believed that such ocular discomfort is due to the presence of certain functional groups in these agents. Examples of such agents which produce ocular discomfort include, but are not limited to:β-blockers such as betaxolol; prostaglandins and prostaglandin derivatives; muscarinics such as pilocarpine; α-adrenergics such as epinephrine, clonidine and apraclonidine; cholinergics such as carbachol; and non-steroidal anti-inflammatory drugs ("NSAIDs") such as diclofenac and suprofen.

There have been a number of attempts to formulate topical ophthalmic compositions to reduce the inherent discomfort associated with these ophthalmic agents. Such attempts include those described in U.S. Pat. No. 4,559,343 (Han et al.), U.S. Pat. No. 4,911,920 (Jani et al.), U.S. Pat. No. 5,093,126 (Jani et al.), and U.S. Pat. No. 5,212,162 (Missel et al.). Han et al. describe the addition of xanthine derivatives, such as caffeine, to decrease the stinging associated with topical ocular application of NSAIDs. The two Jani et al. references teach the addition of certain ion-exchange resins to compositions of β-blockers to increase comfort and to provide sustained release. Missel et al. teach combinations of gelling polysaccharides and finely-divided drug carrier substrates ("DCS") which provide comfortable and sustained release ophthalmic compositions.

In addition, U.S. Pat. No. 4,960,799 (Nagy), discloses storage stable aqueous ophthalmic compositions containing diclofenac and/or its pharmaceutically acceptable salts. The Nagy compositions include EDTA and a solubilizer such as ethoxylated castor oil.

SUMMARY OF THE INVENTION

It has now been unexpectedly discovered that the addition of certain vitamin E tocopheryl derivatives to ophthalmic compositions renders such compositions very comfortable and non-irritating. It has also been discovered that these vitamin E derivatives greatly enhance the aqueous solubility of many compounds which are only sparingly soluble in aqueous compositions.

DETAILED DESCRIPTION OF THE INVENTION

Vitamin E tocopheryl derivatives are water-soluble, biologically-active vitamin E analogues. These vitamin E

derivatives have been used as alternatives to vitamin E, especially where water-solubility is desired. In addition, U.S. Pat. No. 3,102,078 describes the use of these derivatives to solubilize naturally-occurring water-insoluble vitamins, such as vitamins A, D and E. The use of these vitamin E derivatives to enhance the absorption of vitamin A and cyclosporin have also been reported. See, for example, Sokol, R. J. et al., "Improvement of Cyclosporin Absorption in Children after Liver Transplantation by Means of Water-soluble Vitamin E," *The Lancet*, 338:212–215 (1991), and Argao, E. A. et al., "d-α-Tocopheryl Polyethylene Glycol-1000 Succinate Enhances the Absorption of Vitamin D in Chronic Cholestatic Liver Disease of Infancy and Childhood," *Pediatric Res.*, 31(2):146–150 (1992).

The vitamin E tocopheryl derivatives useful in the compositions of the present invention are highly water-soluble polyoxyalkylene glycol esters of vitamin E tocopheryl esters of a dicarboxylic acid. Representative esters of this type include the polyoxyethylene glycol esters of vitamin E tocopheryl esters of a dicarboxylic acid wherein the polyoxyethylene glycol moiety of the ester (sometimes merely referred to as the polyoxyethylene glycol moiety of the ester) has a molecular weight in the range from about 600 to about 6000, preferably in the range from about 600 to about 1500. Such esters and methods for their preparation are disclosed in U.S. Pat. No. 2,680,749 (Cawley et al.). The most preferred ester is the α-tocopheryl polyoxyethylene glycol (1000) succinate, a polyoxyethylene glycol ester of α-tocopheryl succinate wherein the polyoxyethylene glycol moiety of the molecule has an average molecular weight of about 1000.

In general, one or more vitamin E derivatives are used in the compositions of the present invention in an amount less than about 30 percent by weight (wt %). If the vitamin E derivatives are used as solubilizing agents, it is preferred to use an amount between about 0.1 and about 20 wt %, most preferably between about 0.1 and about 5 wt %. When the vitamin E derivatives are used to enhance comfort, it is preferred to use an amount between about 0.1 and about 20 wt %, most preferably between about 0.5 and about 10 wt %.

Suitable ophthalmic agents which may be included in the compositions of the present invention and administered via the method of the present invention include, but are not limited to, the racemic and enantiomeric forms and ophthalmically acceptable salts and esters of following types of compounds:

glaucoma agents, such as: β-blockers (e.g., betaxolol, timolol, and carteolol); α-agonists (e.g., apraclonidine and related 2-substituted amino imidazolines); carbonic anhydrase inhibitors; dopamine agonists and antagonists; miotic cholinergics (e.g., pilocarpine and carbachol); prostaglandins and prostaglandin derivatives; ACE inhibitors; steroids (e.g., glucocorticoids and angiostatic steroids); and calcium channel blockers;

anti-hypertensives;

non-steroidal anti-inflammatory agents, including but not limited to those classified as aryl- or heteroaryl- alkanoic acids such as diclofenac, flurbiprofen, suprofen, ketorolac, indomethacin and ketoprofen;

steroidal anti-inflammatory agents, such as fluoromethalone, dexamethasone, prednisolone, tetrahydrocortisol and triamcinolone;

anti-bacterials and anti-infectives, such as aminoglycosides (e.g., tobramycin); quinolones (e.g., ciprofloxacin and ofloxacin); beta-lactams (e.g., cephalosporins such as cefamandole);

anti-fungals, such as natamycin;
anti-virals, such as acyclovir and ganciclovir;
anti-cataract agents and anti-oxidants;
anti-allergics;
anti-metabolites, such as 5-fluorouracil (5-FU) and methotrexate;
immunosuppressants, such as cyclosporin, FK-506 and leflunimide;
growth factors such as EGF, FGF, PDGF; and
prodrugs of the drug classes listed above.

Combinations of ophthalmic agents may also be used in the compositions of the present invention. Further, in formulations without ophthalmic agents, the present invention may also serve to supplement tears in the prevention or treatment of dry eye.

The compositions of the present invention may additionally include other ophthalmically acceptable components: for example, buffers (e.g., phosphate, borate and citrate), chelating agents (e.g., EDTA), preservatives, (e.g., benzalkonium chloride, Polyquad® and Dymed®) and tonicity agents (e.g., sodium chloride and mannitol). The compositions of the present invention may also include viscosity modifying agents such as: cellulosic ethers, such as, hydroxypropyl methyl cellulose (HPMC), hydroxyethyl cellulose (HEC), ethyl hydroxyethyl cellulose, hydroxypropyl cellulose, methyl cellulose, and carboxymethyl cellulose; carbomers (Carbopol); polyvinyl alcohol; polyvinyl pyrrolidone; alginates; carrageenans; and guar, karaya, agarose, locust bean, tragacanth and xanthan gums. The concentration of such viscosity modifiers will vary between about 0.1 to about 5 wt %, but such formulations will generally have a viscosity between about 10 and about 1000 centipoise.

The ophthalmic compositions containing TPGS may additionally contain polymers which will undergo sol-to-gel transition upon exposure to physical or chemical stimuli, such as changes in pH, ion concentration, and/or temperature.

The ophthalmic agents contained in the compositions of the present invention may optionally be encapsulated in microparticles. These loaded microparticles can be dispersed in aqueous vehicles containing TPGS to improve comfort. In addition, water-soluble or water-insoluble complexes of the ophthalmic agent can be incorporated in a vehicle containing TPGS. Example of water-soluble complexes include traditional complexes formed between the ophthalmic agent and caffeine, cyclodextrins, salicylates, benzoates. Examples of water insoluble complexes include ophthalmic agent - drug resin complexes.

The following examples are presented to illustrate further various aspects of the present invention, but are not intended to limit the scope of the invention in any respect.

EXAMPLE 1

The following formulations are representative of preferred compositions of the present invention.

	FORMULATION (wt %)						
INGREDIENTS	A	B	C	D	E	F	G
Sodium Diclofenac	0.1	0.1	0.1	0.1	0.1	—	0.1
Dexamethasone	—	—	—	—	—	0.1	—
Vitamin E TPGS (1000)	3.0	3.0	3.0	3.0	3.0	3.0	3.0
Tromethamine	0.23	0.23	0.23	1.2	1.2	—	0.23
Boric Acid	1.0	0.1	0.1	1.5	1.5	—	1.0

-continued

	FORMULATION (wt %)						
INGREDIENTS	A	B	C	D	E	F	G
Mannitol	4.0	—	—	3.0	4.0	—	4.0
Benzalkonium Chloride	0.01	0.01	0.01	0.01	0.01	0.01	—
NaCl	—	0.7	0.7	—	—	—	—
Disodium EDTA	0.1	0.1	0.1	0.1	0.1	—	—
HPMC	—	0.1	0.3	0.1	0.3	—	—
Arginine	—	—	—	0.5	—	—	—
HCl and/or NaOH	pH to 7.4						
Purified Water	q.s. 100%						

Preparation:

Formulation D was prepared as follows, and Formulations A–C and E–G were prepared similarly.

A 10% (w/v) stock solution of vitamin E TPGS was prepared as follows. Approximately 150 g of vitamin E TPGS was melted in a beaker by heating on a hot plate with stirring to ensure homogeneity. About 100 grams (g) of the molten TPGS was then added into 800 milliliters (mL) of near-boiling double distilled water. This mixture was stirred and allowed to cool to room temperature to ensure complete dissolution. Sufficient water was then added to the above solution to make a liter of stock solution.

Sodium diclofenac (0.3 g) was added to 90 mL of 10% TPGS stock solution. After complete dissolution of the diclofenac, the each of following ingredients were sequentially added to the solution with stirring so that each ingredient was completely dissolved before the next ingredient was added: 1.5 g of arginine, 9.0 g of mannitol, 4.5 g of boric acid, 3.6 g of trumethamine and 0.3 g of edetate sodium. To the above solution was added 6.0 mL of 0.5% solution of benzalkonium chloride, followed by the addition of 15 mL of 2% solution of HPMC. An additional 150 mL of water were added and the pH of the formulation adjusted to 7.4 with HCl and/or NaOH. To the resulting solution, enough water was added to bring the total solution volume to 300 mL. The osmolality of the final solution was about 300 mOsm/kg.

The 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 spirit 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.

What is claimed is:

1. A method for treating or controlling ocular inflammation, comprising the topical ocular application of an ophthalmic composition wherein the ophthalmic composition comprises:

a therapeutically effective amount of one or more ophthalmic agents selected from the group consisting of non-steroidal anti-inflammatory agents and steroidal anti-inflammatory agents;

an amount of a polyoxyalkylene glycol ester of a vitamin E tocopheryl ester of a dicarboxylic acid effective to reduce the discomfort and irritation associated with topical ophthalmic administration of said ophthalmic agent; and

an ophthalmically acceptable aqueous vehicle, wherein the aqueous vehicle does not comprise liposomes.

2. The method of claim 1, wherein ophthalmic agent is a the non-steroidal anti-inflammatory agent comprising an

aryl- or heteroaryl-alkanoic acid, or an ophthalmically acceptable salt, ester or amide thereof.

3. The method of claim 2, wherein the non-steroidal anti-inflammatory agent is selected from the group consisting of diclofenac and its ophthalmically acceptable salts, esters or amides.

4. A method for improving comfort and reducing irritation in ophthalmic compositions containing one or more ophthalmic agents which are irritating to the eye, comprising the step of adding to the ophthalmic composition an amount of a polyoxyalkylene glycol ester of a vitamin E tocopheryl ester of a dicarboxylic acid effective to reduce the discomfort and irritation associated with topical ophthalmic administration of said ophthalmic agent.

5. The method of claim 4, wherein the polyoxyalkylene glycol ester of a vitamin E tocopheryl ester of a dicarboxylic acid is selected from one or more polyoxyethylene glycol esters of a vitamin E tocopheryl ester of succinic acids wherein the polyoxyethylene glycol moiety of the ester has a molecular weight in a range between about 600 and about 6000.

6. The method of claim 5, wherein the polyoxyethylene glycol moiety of the ester has an average molecular weight of about 1000.

7. The method of claim 4, wherein the concentration of polyoxyalkylene glycol ester of a vitamin E tocopheryl ester of a dicarboxylic acid is less than about 30 percent by weight.

8. The composition of claim 7, wherein the concentration of polyoxyalkylene glycol ester of a vitamin E tocopheryl ester of a dicarboxylic acid is between about 0.1 and about 20 percent by weight.

9. The composition of claim 8, wherein the concentration of polyoxyalkylene glycol ester of a vitamin E tocopheryl ester of a dicarboxylic acid is between about 0.5 and about 10 percent by weight.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 5,886,030
DATED : March 23, 1999
INVENTOR(S) : Maniar

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

Claim 8 should read: "The method of claim 7 ....." instead of "The composition of claim 7 ....."

Claim 9 should read: "The method of claim 8 ....." instead of "The composition of claim 8 ....."

Signed and Sealed this

Twenty-eighth Day of September, 1999

Attest:

Q. TODD DICKINSON

Attesting Officer *Acting Commissioner of Patents and Trademarks*

IFW

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MAR 2 4 2010

CERTIFICATE OF FACSIMILE TRANSMISSION

I hereby certify that this paper is being facsimile transmitted to the Patent and Trademark Office on the date shown below.

Warren Cheek
Typed or printed name of person signing certificate

Signature

March 24, 2010
Date

FACSIMILE COVER SHEET

Date: March 24, 2010

To: **Examiner Donna A. Jagoe, Group Art Unit 1614**

Fax: 571-273-8300

From: Warren M. Cheek

Number of pages being transmitted, including this cover sheet: 19

Please direct all questions concerning the transmittal of these pages to: Donna King/Warren Cheek

RE: Serial No. 10/525,006 (Shirou SAWA et al.), filed March 28, 2005,
Confirmation No. 1756

PAGE 1/19 * RCVD AT 3/24/2010 4:34:20 PM [Eastern Daylight Time] * SVR:USPTO-EFXRF-6/30 * DNIS:2738300 * CSID:202 721 8250 * DURATION (mm-ss):03-32

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 03/24/2010	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE ($)	SMALL ENTITY ADDITIONAL FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	* 25	Minus	** 45	= 0	X $ =		OR	X $52=	0
Independent (37 CFR 1.16(h))	* 4	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:
/KAREN T. WASHINGTON/

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	03/24/2010	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE ($)	SMALL ENTITY ADDITIONAL FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 25	Minus	** 45	= 0	X $ =		OR	X $52=	0
	Independent (37 CFR 1.16(h))	* 4	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:
/KAREN T. WASHINGTON/

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 03/02/2010

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
1619	

NOTIFICATION DATE	DELIVERY MODE
03/02/2010	ELECTRONIC

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

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

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

ddalecki@wenderoth.com
eoa@wenderoth.com

Interview Summary	Application No.	Applicant(s)	
	10/525,006	SAWA ET AL.	
	Examiner	Art Unit	
	Donna Jagoe	1619	

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

(1) *Donna Jagoe*.

(2) *Jim Currie*.

(3)*Ken Jenkins and Warren Cheek*.

(4)*Martin Voet*.

Date of Interview: *16 February 2010*.

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: *the claims in general*.

Identification of prior art discussed: *Hellberg et al. 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: *Applicant pointed out the difference between the prior art and the instant claims. There was a discussion regarding the Hellberg ester compounds drawn tyloxapol used for ball milling, not as a cosolvent* .

(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.

/Donna Jagoe/ Examiner, Art Unit 1619	/YVONNE L. EYLER/ Supervisory Patent Examiner, Art Unit 1619

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.

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Alexandria, Virginia 22313-1450
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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 12/24/2009

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
1619	

MAIL DATE	DELIVERY MODE
12/24/2009	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	1619	

-- 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 *05 October 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 _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on October 5, 2009 has been entered.

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.

Priority

Receipt is acknowledged of the Japanese priority application and certified translation submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

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.

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, Yvonne (Bonnie) Eyler can be reached on (571) 272-0871. 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.

/YVONNE L. EYLER/
Supervisory Patent Examiner, Art Unit 1619

Donna Jagoe /D. J./
Examiner
Art Unit 1619

December 17, 2009

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

SEARCHED

Class	Subclass	Date	Examiner
514	567	5/30/09	dj
424	486	5/30/09	dj
	updated	12/17/09	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
WEST see attached search history transcript	12/17/09	dj

INTERFERENCE SEARCH

Class	Subclass	Date	Examiner

/Donna Jagoe/ Examiner.Art Unit 1614	

U.S. Patent and Trademark Office Part of Paper No. : 20091217

WEST Search History for Application 10525006

Creation Date: 2009121717:13

bromfecanPGPB, USPT, USOC, EPAB, JPAB, DWPI ADJ YES 05-30-2009
bromfenacPGPB, USPT, USOC, EPAB, JPAB, DWPI ADJ YES 05-30-2009
tyloxapolPGPB, USPT, USOC, EPAB, JPAB, DWPI ADJ YES 05-30-2009
sterilePGPB, USPT, USOC, EPAB, JPAB, DWPI ADJ YES 05-30-2009
isotonicPGPB, USPT, USOC, EPAB, JPAB, DWPI ADJ YES 05-30-2009
pHPGPB, 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

Prior Art Searches

Query	DB	Op.	Plur.	Thes.	Date
bromfecan	PGPB, USPT, USOC, EPAB, JPAB, DWPI	ADJ	YES		12-17-2009
bromfenac	PGPB, USPT, USOC, EPAB, JPAB, DWPI	ADJ	YES		12-17-2009
tyloxapol	PGPB, USPT, USOC, EPAB, JPAB, DWPI	ADJ	YES		12-17-2009
sterile	PGPB, USPT, USOC, EPAB, JPAB, DWPI	ADJ	YES		12-17-2009
isotonic	PGPB, USPT, USOC, EPAB, JPAB, DWPI	ADJ	YES		12-17-2009
pH	PGPB, USPT, USOC, EPAB, JPAB, DWPI	ADJ	YES		12-17-2009
(bromfenac) and (tyloxapol) and (sterile) and (isotonic) and (pH)	PGPB, USPT, USOC, EPAB, JPAB, DWPI	ADJ	YES		12-17-2009

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 10/08/2009

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
10/08/2009	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.

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

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

(1) *Donna Jagoe*. (3)_____.

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

Date of Interview: *07 October 2009*.

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: *exemplary claims 41 and 63*.

Identification of prior art discussed: *Hellberg et al., Nolan et al., Gamache et al.*.

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: *Hellberg teaches any NSAIA including bromfenac covalently linked to an antioxidant. Applicant presented arguments that there is no motivation to replace the Hellberg compound with the Nolan compound.*.

(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.

/Donna Jagoe/ Examiner, Art Unit 1614	

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.

REQUEST for CONTINUED EXAMINATION (RCE) TRANSMITTAL

Address to:
Mail Stop RCE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Application Number	10/525,006
Filing Date	March 28, 2005
First Named Inventor	Shirou SAWA et al.
Group Art Unit	1614
Examiner Name	Donna A. Jagoe
Attorney Docket Number	2005_0232A
Confirmation No.	1756

This is a Request for Continued Examination (RCE) under 37 C.F.R. § 1.114 of the above-identified application.
Request for Continued Examination (RCE) practice under 37 CFR 1.114 does not apply to any utility or plant application filed prior to June 8, 1995, or to any design application. See Instruction Sheet for RCEs (not to be submitted to the USPTO) on page 2.

1. **Submission required under 37 C.F.R. § 1.114 – Note: If the RCE is proper, any previously filed unentered amendments and amendments enclosed with the RCE will be entered in the order in which they were filed unless applicant instructs otherwise. If applicant does not wish to have any previously filed unentered amendment(s) entered, applicant must request non-entry of such amendment(s).**
   a. [ ] Previously submitted. If a final Office Action is outstanding, any amendments filed after the final Office Action may be considered as a submission even if this box is not checked.
      I. [ ] Please consider the arguments in the Appeal Brief or Reply Brief previously filed on
      II. [ ] Other

   b. [X] Enclosed:
      I. [X] Amendment/Reply
      II. [ ] Affidavit(s)/Declaration(s)
      III. [ ] Information Disclosure Statement (IDS)
      IV. [X] Other - Submission of verified English translation of JP 2003-012427

2. **Miscellaneous**
   a. [ ] Suspension of action on the above-identified application is required under 37 C.F.R. § 1.103(c) for a period of months (period of suspension shall not exceed 3 months; Fee under 37 C.F.R. § 1.17(i) required).

   b. [ ] Other

3. **Fees (The RCE fee under 37 C.F.R. § 1.17(e) is required by 37 C.F.R. § 1.114 when the RCE is filed.)**
   a. [X] The Director is hereby authorized to charge the following fees to Deposit Account No. 23-0975.
      I. [ ] RCE fee required under 37 C.F.R. § 1.17(e)
      II. [ ] Extension of time fee (37 C.F.R. § 1.136 and § 1.17)
      III. [X] Other: Any deficiency or to credit any over payment associated with this filing

   b. [] Check in the amount of $ enclosed

   c. [X] Payment is made by Credit Card in the amount of $940.00. (Credit Card Payment Form Enclosed)
      I. [X] RCE fee required under 37 C.F.R. § 1.17(e)
      II. [X] Extension of time fee (37 C.F.R. § 1.136 and § 1.17)
      III. [ ] Other

4. CORRESPONDENCE ADDRESS

CUSTOMER NO.
000513

By: Warcheek

Warren M. Cheek
Registration No. 33,367

WENDEROTH, LIND & PONACK, L.L.P.
1030 15th Street, N.W., Suite 400 East
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Phone:(202) 721-8200
Fax:(202) 721-8250

10/06/2009 SZEWDIE1 00000028 10525006
02 FC:1251 130.00 OP

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**

PRELIMINARY AMENDMENT

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

Sir:

Please amend the above-identified application as follows:

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.

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 formulated for ophthalmic administration~~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 formulated for ophthalmic administration~~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 formulated for ophthalmic administration~~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 formulated for ophthalmic administration~~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 formulated for ophthalmic administration~~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 formulated for ophthalmic administration~~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 formulated for ophthalmic administration~~in the form of an eye drop~~.

REMARKS

A verified English translation of the Japanese priority application is concurrently submitted herewith under separate cover letter.

In addition, claims 19, 39-41, 61-63 have been amended as suggested by the Examiner in the Official Action dated June 3, 2009.

Accordingly, the rejection of the claims under 35 USC 112, second paragraph, is deemed to be overcome.

Applicants express their appreciation to the Examiner for the personal interview scheduled for October 7, 2009.

Respectfully submitted,

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October 5, 2009

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**

SUBMISSION OF VERIFIED ENGLISH TRANSLATION

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

Sir:

Submitted herewith is a verified English translation of the Japanese priority application no. 2003-012427 filed January 21, 2003.

Respectfully submitted,

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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.

VERIFICATION OF TRANSLATION

I, Takeshi Takemori, of 1-2-512, Denpo 1-chome, Osaka-shi, OSAKA 554-0002 JAPAN, state the following:

I am fluent in both the English and Japanese languages and capable of translating documents from one into the other of these languages.

The attached document is a true and accurate English translation to the best of my knowledge and belief of the certified copy of Japanese Patent Application No. 2003-012427 filed on January 21, 2003.

I state that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true.

Signature: Takeshi Takemori

Takeshi Takemori

Date: September 3, 2009

JAPAN PATENT OFFICE

This is to certify that the annexed is a true copy of the following application as filed with this Office.

Date of Application: January 21, 2003

Application Number: JP2003-012427
[ST. 10/C]: [JP2003-012427]

Applicant(s): SENJU PHARMACEUTICAL CO., LTD.

February 19, 2004

Commissioner, Japan Patent Office Yasuo IMAI

Certificate No. 2004-3010925

[Name of Document] Patent application

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[Filing Date] January 21, 2003

[Addressee] To the Commissioner of the Patent Office

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A61P 27/02

A61P 27/16

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[Indication of Fee]

[Deposit Account Number] 004167

[Fee] 21,000 yen

[List of Annexed Document(s)]

[Name of matter] Specification 1

[Name of matter] Abstract 1

[General Power of Attorney Number] 0104918

[Proof] Yes

[Name of Document] Specification

[Title of the Invention] AQUEOUS LIQUID PREPARATION CONTAINING 2-AMINO-3-(4-BROMOBENZOYL)PHENYLACETIC ACID

[Scope of Claims]

[Claim 1] An aqueous liquid preparation comprising 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof, and an alkyl aryl polyether alcohol type polymer or a polyethylene glycol fatty acid ester.

[Claim 2] The aqueous liquid preparation according to claim 1, wherein the alkyl aryl polyether alcohol type polymer has a polymerization degree of 3 to 10, the alkyl contains 1 to 18 carbon atoms, the aryl is a phenol residue, and the polyether alcohol is represented by the formula $(CH_2CH_2O)_xH$ in which X is an integer of 5 to 100.

[Claim 3] The aqueous liquid preparation according to claim 1 or 2, wherein the alkyl aryl polyether alcohol type polymer is tyloxapol.

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

[Claim 5] The aqueous liquid preparation according to claim 1 or 4, wherein the polyethylene glycol fatty acid ester is polyethylene glycol monostearate.

[Claim 6] The aqueous liquid preparation according to any one of claims 1 to 3, wherein the concentration of the alkyl aryl polyether alcohol type polymer is selected from a range of minimum concentration of 0.01 w/v % to maximum concentration

of 0.5 w/v %.

[Claim 7] The aqueous liquid preparation according to any one of claims 1, 2 and 4, wherein the concentration of the polyethylene glycol fatty acid ester is selected from a range of minimum concentration of 0.02 w/v % to maximum concentration of 0.1 w/v %.

[Claim 8] The aqueous liquid preparation according to any one of claims 1 to 7, wherein the concentration of the 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof is 0.01 to 0.5 w/v %.

[Claim 9] The aqueous liquid preparation according to any one of claims 1 to 8, wherein benzalkonium chloride is contained as a preservative.

[Claim 10] The aqueous liquid preparation according to any one of claims 1 to 9, wherein the pharmacologically acceptable salt of 2-amino-3-(4-bromobenzoyl)phenylacetic acid is a sodium salt.

[Claim 11] The aqueous liquid preparation according to any one of claims 1 to 10, wherein the pH of the aqueous liquid preparation is within a range of 7 to 9.

[Claim 12] The aqueous liquid preparation according to claim 11, wherein the pH of the aqueous liquid preparation is within a range of 7.5 to 8.5.

[Claim 13] The aqueous liquid preparation according to any one of claims 1 to 12, wherein the aqueous liquid preparation is an eye drop.

[Claim 14] The aqueous liquid preparation according to

any one of claims 1 to 12, wherein the aqueous liquid preparation is a nasal drop.

[Claim 15] An eye drop comprising sodium 2-amino-3-(4-bromobenzoyl)phenylacetate hydrate and 0.01 to 0.5 w/v % of tyloxapol.

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

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

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

[Detailed Description of the Invention]

[0001]

[Technical Field to Which the Invention Pertains]

The present invention relates to an aqueous liquid preparation containing 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof. More particularly, the present invention relates to an aqueous liquid preparation containing 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof and an alkyl aryl polyether alcohol type polymer or a polyethylene glycol fatty acid ester.

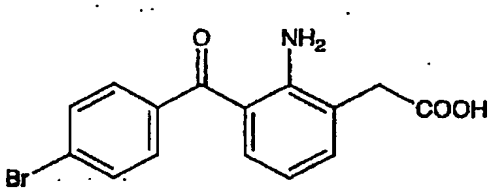
[0002]

[Conventional Art]

Benzoylphenylacetic acid derivatives including bromfenac (generic name) of formula (I):

[0003]

[Chemical Formula 1]



[0004]

of which chemical name is 2-amino-3-(4-bromobenzoyl) phenylacetic acid are known (See Patent Literature 1). 2-Amino-3-(4-bromobenzoyl)phenylacetic acid, its pharmacologically acceptable salt and a hydrate thereof are known as a non-steroidal anti-inflammatory agent, and they are effective against inflammatory diseases of anterior or posterior segment of the eye, such as blepharitis, conjunctivitis, scleritis, and postoperative inflammation in

the field of ophthalmology, and its sodium salt has been practically used in the form of eye drops (See Non-patent Literature 1).

[0005]

The eye drop as mentioned above is designed to stabilize 2-amino-3-(4-bromobenzoyl)phenylacetic acid by means of addition of a water-soluble polymer (e.g. polyvinylpyrrolidone, polyvinyl alcohol, etc.) and a sulfite (e.g. sodium sulfite, potassium sulfite, etc.)(See Patent Literature 3).

In addition, as an eye drop other than the above-mentioned one, there is reported a stable ophthalmic composition which comprises incorporating an antibacterial quaternary ammonium polymer and boric acid into an acidic ophthalmic agent. The acidic agent includes, for example, 2-amino-3-(4-bromobenzoyl)phenylacetic acid (See Patent Literature 4).

[Patent Literature 1] JP-A-23052/1977

[Patent Literature 2] JP-A-126124/1987

[Patent Literature 3] Japanese patent No. 2,683,676

[Patent Literature 4] Japanese patent No. 2,954,356, column 6, lines 26-27, line 45

[Non-patent Literature 1] "New Drugs in Japan, 2001", 2001 Edition, Published by Yakuji Nippo Ltd., May 11, 2001, p.27-29

[0007]

[Problem to be Solved by the Invention]

It is an object of the present invention to provide an aqueous liquid preparation comprising 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically

acceptable salt thereof or a hydrate thereof, which is stable within a pH range giving no irritation to eyes and has a sufficient preservative effect.

[0008]

Another object of the invention is to provide a method for stabilizing an aqueous liquid preparation of 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof.

[0009]

Further, another object of the invention is to provide a method for inhibiting decrease in preservative effect of a preservative in an aqueous liquid preparation comprising 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof and the preservative.

[0010]

[Means for Solving the Problem]

As a result of various studies, the inventors of the present invention have found that, by adding an alkyl aryl polyether alcohol type polymer such as tyloxapol, or a polyethylene glycol fatty acid ester such as polyethylene glycol monostearate to an aqueous liquid preparation of 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof, the aqueous solution becomes stable within a pH range giving no irritation to eyes and has a sufficient preservative effect. The inventors of the present invention have further studied extensively and completed the present invention.

[0011]

Namely, the present invention relates to:

(1) An aqueous liquid preparation comprising 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof, and an alkyl aryl polyether alcohol type polymer or a polyethylene glycol fatty acid ester,

(2) The aqueous liquid preparation according to the above (1), wherein the alkyl aryl polyether alcohol type polymer has a polymerization degree of 3 to 10, the alkyl contains 1 to 18 carbon atoms, the aryl is a phenol residue, and the polyether alcohol is represented by the formula $(CH_2CH_2O)_xH$ in which X is an integer of 5 to 100,

(3) The aqueous liquid preparation according to the above (1) or (2), wherein the alkyl aryl polyether alcohol type polymer is tyloxapol,

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

(5) The aqueous liquid preparation according to the above (1) or (4), wherein the polyethylene glycol fatty acid ester is polyethylene glycol monostearate,

(6) The aqueous liquid preparation according to any one of the above (1) to (3), wherein the concentration of the alkyl aryl polyether alcohol type polymer is selected from a range of minimum concentration of 0.01 w/v % to maximum concentration of 0.5 w/v %,

(7) The aqueous liquid preparation according to any one of the

above (1), (2) and (4), wherein the concentration of the polyethylene glycol fatty acid ester is selected from a range of minimum concentration of 0.02 w/v % to maximum concentration of 0.1 w/v %,

(8) The aqueous liquid preparation according to any one of the above (1) to (7), wherein the concentration of the 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof is 0.01 to 0.5 w/v %,

(9) The aqueous liquid preparation according to any one of the above (1) to (8), wherein benzalkonium chloride is contained as a preservative,

(10) The aqueous liquid preparation according to anyone of the above (1) to (9), wherein the pharmacologically acceptable salt of 2-amino-3-(4-bromobenzoyl)phenylacetic acid is a sodium salt,

(11) The aqueous liquid preparation according to any one of the above (1) to (10), wherein the pH of the aqueous liquid preparation is within a range of 7 to 9,

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

(13) The aqueous liquid preparation according to any one of the above (1) to (12), wherein the aqueous liquid preparation is an eye drop,

(14) The aqueous liquid preparation according to any one of the above (1) to (12), wherein the aqueous liquid preparation is a nasal drop,

(15) An eye drop comprising sodium 2-amino-3-(4-

bromobenzoyl)phenylacetate hydrate and 0.01 to 0.5 w/v % of tyloxapol,

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

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

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

[0012]

In the present invention, the pharmacologically acceptable salt of 2-amino-3-(4-bromobenzoyl)phenylacetic acid includes, for example, an alkali metal salt such as sodium salt and potassium salt, and an alkaline earth metal salt such as calcium salt and magnesium salt, among which sodium salt is

especially preferable.

[0013]

2-Amino-3-(4-bromobenzoyl)phenylacetic acid and its pharmacologically acceptable salt can be prepared according to the method as described in, for example, Patent Literature 1 or by a similar method thereof. These compounds can be obtained as their hydrate depending on synthetic conditions and recrystallization conditions. The hydrate includes 3/2 hydrate.

[0014]

In the aqueous liquid preparation of the present invention, the content of 2-amino-3-(4-bromobenzoyl) phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof is usually about 0.01 to 0.5 w/v %, preferably about 0.05 to 0.2 w/v %, especially about 0.1 w/v %, and the content is appropriate varied depending on the purpose of use and the degree of disease to be treated.

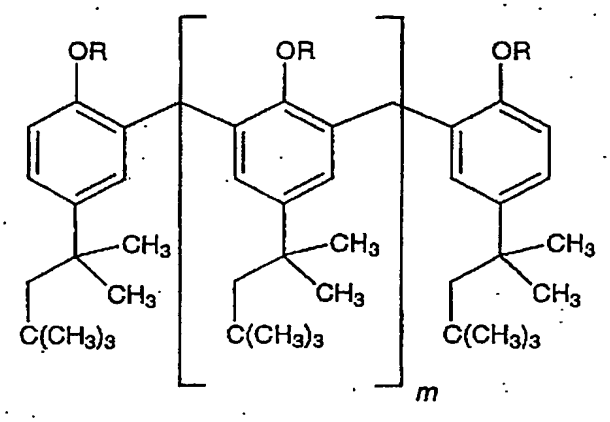
[0015]

The carbon number of alkyl in an alkyl aryl polyether alcohol type polymer (polymerization degree: 3 to 10) which is a non-ionic surfactant used as a stabilizer for 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof is approximately 1 to 18. Specifically, the alkyl group includes, for example, methyl, ethyl, propyl, isopropyl, cyclopropyl, butyl, isobutyl, sec-butyl, tert-butyl, cyclobutyl, pentyl, isopentyl, neopentyl, tert-pentyl, 1-ethylpropyl, 4-methylpentyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 1,2-dimethylbutyl,

2-ethylbutyl, cyclopentyl, hexyl, cyclohexyl, heptyl, isoheptyl, octyl, isooctyl, nonyl, isononyl, decyl, isodecyl, undecyl, isoundecyl, dodecyl, isododecyl, tridecyl, isotridecyl, tetradecyl, isotetradecyl, pentadecyl, isopentadecyl, hexadecyl, isohexadecyl, heptadecyl, isoheptadecyl, octadecyl, isooctadecyl, and isomers thereof, among which 1,1,3,3-tetramethylbutyl which is an isomer of octyl groups is especially preferable. The above-mentioned aryl can be preferably a phenol residue. The above-mentioned polyether alcohol can be represented by the formula $(CH_2CH_2O)_xH$ in which X is an integer of 5 to 100, preferably 5 to 30, more preferably 8 to 10. The average polymerization degree is preferably about 3 to 10. Among the above-mentioned alkyl aryl polyether alcohol type polymers, tyloxapol having the following structure is especially preferable.

[0016]

[Chemical Formula 2]



$R = (CH_2CH_2O)_xH$

$x = 8 \cdot 10$

$m < 6$

[0017]

The fatty acid of the polyethylene glycol fatty acid ester which is a non-ionic surfactant used as a stabilizer for 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof can be preferably a fatty acid having the carbon number of 12 to 18. Specific examples of such polyethylene glycol fatty acid esters are polyethylene glycol monostearate, polyethylene glycol monolaurate, polyethylene glycol monooleate, polyethylene glycol diisostearate, polyethylene glycol dilaurate, polyethylene glycol dioleate, and the like. Among these compounds, polyethylene glycol monostearate is preferable, and polyoxyl 40 stearate is especially preferable. The polyoxyl 40 stearate is a monostearic acid ester of an ethylene oxide condensed polymer, and can be represented by the formula $C_{17}H_{35}COO(CH_2CH_2O)_nH$ which is a non-ionic surfactant and n is about 40.

[0018]

Although the content of the alkyl aryl polyether alcohol type polymer in the aqueous liquid preparation of the present invention depends on the kind of compounds used, the minimum concentration is about 0.01 w/v % and the maximum concentration is about 0.5 w/v %. With respect to the tyloxapol content, for example, the minimum content is about 0.01 w/v %, 0.02 w/v % or 0.03 w/v %, and the mamximum content is about 0.05 w/v %, 0.1 w/v %, 0.3 w/v % or 0.5 % w/v, and preferably the minimum content is about 0.02 w/v % and the maximum content is about 0.05 w/v %.