# Part 3
# to
# EXHIBIT G

10236566.090602

[ ] English Translation Docume *'applicable)*
[ x] Information Disclosure Statement/PTO-1449 [ ] Copies of _ IDS Cited Reference(s)
[ x] Preliminary Amendment
[x] Acknowledgment postcard
[ ] Copy from prior application (37 CFR 1.63(d)) *(for continuation/divisional application only)*
[x ] Certificate of Mailing by Express Mail
[ ] Certified Copy of Priority Document(s) *(if foreign priority is claimed)*

**Fee Calculation and Transmittal**

** The filing fee is calculated on the basis of the claims existing in the prior application as amended by the accompanying preliminary amendment noted above.*

| CLAIMS AS FILED | | | | | |
|---|---|---|---|---|---|
| **For** | **#Filed** | **#Allowed** | **#Extra** | **Rate** | **Fee** |
| **Total Claims** | 20 | - 20 = | 0 | X $18.00 | $0.00 |
| **Independent Claims** | 2 | - 3 = | 0 | X $80.00 | $ 0.00 |
| **Multiple Dependent Claims** *(check if applicable)* [ ] | | | | | $ 0.00 |
| | | | | **BASIC FEE** | $740.00 |
| **OTHER FEE** *(specify purpose) ASSIGNMENT RECORDATION FEE* | | | | | |
| (Applicant has small entity status under 37 CFR 1.9 and 1.27) | | | | **SMALL ENTITY STATUS** | – |
| | | | | **TOTAL FILING FEE** | $740.00 |

[ ] A check in the amount of $ __ to cover the filing fee and the assignment fee is enclosed.
[x] The Commissioner is hereby authorized to charge and/or credit Deposit Account Number **01-0885** as described below.
  [x] Charge the amount of **$740.00** as filing fee and assignment fee.
  [x] Credit any overpayment.
  [x] Charge any additional filing fees required under 37 CFR 1.16 and 1.17.

Respectfully Submitted,

Frank J. Uxa
Attorney for Applicants
Registration Number: 25,612

Stout, Uxa, Buyan & Mullins, LLP
4 VENTURE, SUITE 300, IRVINE, CA 92618
*phone* (949) 450-1750; *fax* (949) 450-1764

10235566.090602

#21A
11/1/02

D-2892CON

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
PATENT

In the application of:
Olejnik et al

Serial No. N/A

Filing Date: HEREWITH

For: COMPOSITIONS CONTAINING ALPHA-2-ADRENERGIC AGONIST COMPONENTS

Group Art Unit: N/A

Examiner: N/A

**PRELIMINARY AMENDMENT**

Commissioner for Patents
Washington, DC 20231

Dear Sir:

Please amend the subject application as follows:

**IN THE SPECIFICATION**

Page 1, delete the first paragraph and insert in place thereof:

A1 --This application is a continuation of application Serial No. 09/904,018, filed July 10, 2001 which, in turn, claims the benefit of U.S. Provisional Application Serial No. 60/218,200, filed July 14, 2002. The disclosure of each of the above-noted applications is incorporated in its entirety herein by reference.--

**IN THE CLAIMS**

Cancel Claims 1 to 46, without prejudice.

Add new claims 47 to 66 as follows:

A2 Sub R1 47. (New Claim) A composition comprising;

10236566.090602



water; and

up to about 0.15% (w/v) of 5-bromo-6-(2-imidozolin-2-ylamino)quinoxaline tartrate, the composition having a pH of about 7.0 or greater, and the 5-bromo-6-(2-imidozolin-2-ylamino)quinoxaline tartrate being soluble in the composition at 21°C.

2 ~~48~~. (New Claim) The composition of claim ~~47~~ 1 which includes up to 0.15%(w/v) of 5-bromo-6-(2-imidozolin-2-ylamino)quinoxaline tartrate.

3 ~~49~~. (New Claim) The composition of claim ~~47~~ 1 which includes about 0.15% (w/v) of 5-bromo-6-(2-imidozolin-2-ylamino)quinoxaline tartrate.

4 ~~50~~. (New Claim) The composition of claim ~~47~~ 1 which includes 0.15% (w/v) of 5-bromo-6-(2-imidozolin-2-ylamino)quinoxaline tartrate.

5 ~~51~~. (New Claim) The composition of claim ~~47~~ 1 having a pH of 7.0 or greater.

52. (New Claim) The composition of claim 47 which is ophthalmically acceptable.

53. (New Claim) The composition of claim 47 which further comprises an oxy-chloro component in an amount effective to at least assist in preserving the composition.

7 ~~54~~. (New Claim) The composition of claim ~~53~~ 6 wherein the oxy-chloro component comprises a chlorite component.

6 ~~55~~. (New Claim) The composition of claim ~~47~~ 1 which is

10236566.090602



substantially free of anionic cellulosic derivatives.

9 ~~56~~. (New Claim) The composition of claim ~~47~~ 1 which is substantially free of carboxymethyl cellulose.

All cont'd

57. (New Claim) A composition comprising:
water; and
up to about 0.15% (w/v) of a component selected from the group consisting of 5-bromo-6-(2-imidozolin-2-ylamino)quinoxaline, salts of 5-bromo-6-(2-imidozolin-2-ylamino)quinoxaline, esters of 5-bromo-6-(2-imidozolin-2-ylamino)quinoxaline and mixtures thereof, the composition having a pH of about 7.0 or greater, and the component being soluble in the composition at 21°C.

Sub R3

11 ~~58~~. (New Claim) The composition of claim ~~57~~ 10 which includes up to 0.15% (w/v) of the component.

12 ~~59~~. (New Claim) The composition of claim ~~57~~ 10 which includes about 0.15% (w/v) of the component.

13 ~~60~~. (New Claim) The composition of claim ~~57~~ 10 which includes 0.15% (w/v) of the component.

14 ~~61~~. (New Claim) The composition of claim ~~57~~ 10 having a pH of 7.0 or greater.

7 C

62. (New Claim) The composition of claim 57 which is ophthalmically acceptable.

15 ~~63~~. (New Claim) The composition of claim ~~57~~ 10 which further comprises an oxy-chloro component in an amount effective to at least assist in preserving the composition.

10236566.090602

D-2892CON
Olejnik et al
Page 4

16 ~~64~~. (New Claim) The composition of claim ~~58~~ 15 wherein the oxychloro component comprises a chlorite component.

AP cont'd

17 ~~65~~. (New Claim) The composition of claim ~~57~~ 10 which is substantially free of anionic cellulosic derivatives.

18 ~~66~~. (New Claim) The composition of claim ~~57~~ 10 which is substantially free of carboxymethyl cellulose.

**REMARKS**

The specification has been amended to make reference to prior, related applications.

Claims 1 to 46 have been canceled, without prejudice.

New claims 47 to 66 have been added and are directed to embodiments for which patent protection is sought. Each of these new claims is fully supported by the present specification.

Applicant respectfully requests early and favorable action in the above-identified application.

Respectfully submitted,

Frank J. Uxa
Attorney for Applicant
Reg. No. 25,612
4 Venture, Suite 300
Irvine, CA 92618
(949) 450-1750
Facsimile (949) 450-1764

FJUxa/jm

A

#3

D D-2892CON

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
PATENT

JC979 U.S. PTO
10/236566
09/06/02

In the application of:
Olejnik et al

Group Art Unit: N/A

Serial No. N/A

Examiner: N/A

Filing Date: HEREWITH

For: COMPOSITIONS CONTAINING ALPHA-2-ADRENERGIC AGONIST COMPONENTS

**INFORMATION DISCLOSURE STATEMENT**

Assistant Commissioner for Patents
Washington, DC 20231

Dear Sir:

Applicant wishes to call to the attention of the Examiner the documents cited on the accompanying Form PTO-1449. No concession is made that these documents are prior art, and applicant expressly reserves the right to antedate the documents as may be appropriate. Applicant requests that each of these documents be made of record in the above-identified application.

Some of these documents were cited in related application Application Serial No. 09/904,018, filed July 10, 2001 and Application Serial No. 09/903,962, filed July 10, 2001.

Therefore, no copies of these documents are submitted herewith.

Respectfully submitted,

Frank J. Uxa
Attorney for Applicant
Reg. No. 25,612
4 Venture, Suite 300
Irvine, CA 92618
(949) 450-1750
Facsimile (949) 450-1764

FJUxa/au

JC979 U.S. PTO
10/236566
09/06/02

DOCKET NO.: D-2892CON

THE ENCLOSED PATENT APPLICATION OF OLEJNIK ET AL IS BEING FILED IN ACCORDANCE WITH SECTION 37 CFR 1.10 BY EXPRESS MAIL AND SHOULD BE ACCORDED A FILING DATE OF:

September 6, 2002

SEE THE EXPRESS MAIL CERTIFICATE ATTACHED TO THE APPLICATION.

Sheet 1 of 1

Form PTO-1449

**INFORMATION DISCLOSURE CITATION IN AN APPLICATION**
(Use several sheets if necessary)

DOCKET NO: D-2892CON | APPLN. NO.: N/A

APPLICANT: Olejnik et al

FILING DATE: Herewith | GROUP ART: N/A

09/903962 JC19 U.S. PTO 07/10/2001

## U. S. PATENT DOCUMENTS

| EXAMINER INITIAL | DOCUMENT NUMBER | DATE | NAME | CLASS | SUBCLASS | FILING DATE |
|---|---|---|---|---|---|---|
| RB | 3 2 7 8 4 4 7 | 10/11/66 | McNicholas | | | |
| | 3 8 9 0 3 1 9 | 06/17/75 | Danielewicz et al. | | | |
| | 4 5 3 0 9 2 0 | 07/23/85 | Nestor et al. | | | |
| | 4 8 0 6 5 5 6 | 02/21/89 | Portoghese | | | |
| | 5 0 2 1 4 1 6 | 06/04/91 | Gluchowski | | | |
| | 5 2 0 2 1 2 8 | 04/13/93 | Morella et al. | | | |
| | 5 3 5 2 7 9 6 | 10/04/94 | Haeger et al. | | | |
| | 5 4 5 9 1 3 3 | 10/17/95 | Neufeld | | | |
| | 5 7 0 3 0 7 7 | 12/30/97 | Burke et al. | | | |
| | 5 7 1 9 1 9 7 | 02/17/98 | Kanios et al. | | | |
| | 5 7 2 5 8 8 7 | 03/10/98 | Martin et al. | | | |
| | 5 8 1 4 6 3 8 | 09/29/98 | Lee et al. | | | |
| | 5 8 3 4 5 0 2 | 11/10/98 | Cheng et al. | | | |
| RB | 5 8 9 4 1 1 0 | 11/30/99 | Mosbach et al. | | | |

## FOREIGN PATENT DOCUMENTS

| EXAMINER INITIAL | DOCUMENT NUMBER | DATE | COUNTRY | CLASS | SUBCLASS | TRANSLATION YES | TRANSLATION NO |
|---|---|---|---|---|---|---|---|
| RB | 2 0 4 8 3 1 5 | 02/09/92 | Canada | | | | |
| | 0 6 0 8 9 6 1 | 08/10/94 | European | | | | |
| | 94 / 1 6 6 8 5 | 08/04/94 | International WIPO | | | | |
| | 98 / 4 7 8 7 8 | 10/29/98 | International WIPO | | | | |
| | 99 / 4 3 2 9 9 | 09/02/99 | International WIPO | | | | |
| | 99 / 5 1 2 7 3 | 10/14/99 | International WIPO | | | | |
| | 00 / 1 2 1 9 7 | 03/09/00 | International WIPO | | | | |
| RB | 00 / 1 9 9 8 1 | 04/13/00 | International WIPO | | | | |

## OTHER DOCUMENTS

| | |
|---|---|
| RB | U.S. Patent Application Serial No. 09/903,962, filed July 10, 2001 |

EXAMINER: Rachel M. Bennett

DATE CONSIDERED: 12/10/02

EXAMINER: Initial if citation 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 the applicant.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 10/236,566 | 09/06/2002 | Orest Olejnik | D-2892CON | 3779 |

33197 7590 12/18/2002

STOUT, UXA, BUYAN & MULLINS LLP
4 VENTURE, SUITE 300
IRVINE, CA 92618

| EXAMINER |
|---|
| BENNETT, RACHEL M |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1615 | 4 |

DATE MAILED: 12/18/2002

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

PTO-90C (Rev. 07-01)

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/236,566 | OLEJNIK ET AL. | |
| | Examiner | Art Unit | |
| | Rachel M. Bennett | 1615 | |

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

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 1 MONTH(S) 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 the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- 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 2002* .

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) *47-66* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *47-66* 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).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

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.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**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-1449) Paper No(s) 3 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

U.S. Patent and Trademark Office
PTO-326 (Rev. 04-01) Office Action Summary Part of Paper No. 4

**DETAILED ACTION**

The examiner acknowledges receipt of Preliminary Amendment A and IDS filed 9/6/02.

***Double Patenting***

1. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

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

2. Claims 47-66 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 24-30, 40-43 of copending Application No. 09/904,018. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims are drawn to a composition comprising 5-bromo-6-(2-imidozolin-2-ylamino) quinozaline tartate and 5-bromo-6-(2-imidozolin-2-ylamino) quinozaline in an ophthalmically acceptable formulation comprising an oxy-chloro component while Application 09/904,018 claims a composition comprising a tartate of 5-bromo-6-(2-imidozolin-2-ylamino) quinozaline in an amount effective to provide a therapeutic benefit to a patient to whom the composition is administered and an aqueous liquid carrier component. More generally, application 09/904,018 claims a composition comprising an alpha-2-adrenergic agonist component in an amount effective to provide a therapeutic benefit to a patient to whom the composition is administered; an oxy-chloro component in an effective

amount to at least aid in preserving the composition; and a liquid carrier component, wherein the composition is substantially free of cyclodextrins.

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

3. Claims 47-66 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 35-52 of copending Application No.09/903962. Although the conflicting claims are not identical, they are not patentably distinct from each other because the because the instant claims are drawn to a composition comprising 5-bromo-6-(2-imidozolin-2-ylamino) quinozaline tartate and 5-bromo-6-(2-imidozolin-2-ylamino) quinozaline in an ophthalmically acceptable formulation comprising and oxy-chloro component while Application 09/903,962 claims a composition comprising a tartate of 5-bromo-6-(2-imidozolin-2-ylamino) quinozaline in an amount effective to provide a trerapeutic benefit to a patient to whom the composition is administered, a cholorite component in an effective amount to at least aid in preserving the composition and an aqueous liquid carrier component. More generally, application 09/903962 claims a composition comprising an therapeutically active component in an amount effective to provide a therapeutic benefit to a patient to whom the composition is administered; an oxy-chloro component in an effective amount to at least aid in preserving the composition; and a liquid carrier component, wherein the composition is substantially free of cyclodextrins.

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

***Claim Rejections - 35 USC § 103***

4. 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.

5. Claims 47-66 are rejected under 35 U.S.C. 103(a) as being unpatentable over Burke (US 5215991).

Burke discloses pharmaceutical compositions of alpha 2 agonists and Na+/H+ exchange inhibitors which are useful in lowering intraocular pressure (IOP) and treatment of intraocular hypertension (see abstract). Preferred imidazoline-derived alpha 2 agonists or pharmaceutically acceptable salts thereof are disclosed in col. 3 (see formula). The most preferred imidazoline-derived alpha 2 agonist compounds include 5-bromo-6-(2-imidazolidine-2-ylamino)quinoxaline. Doses of alpha 2 agonist in an ophthalmic preparation effective, non-toxic amount of the agonist in a pharmaceutically acceptable liquid, gel, cream or aqueous or nonaqueous liquid suspension or solution are preferably from about 0.001% to about 1.0% weight/volume. Regardless of the preferred range stated herein, one can determine the most efficacious dose for a particular alpha 2 agonist by carrying out a dose response curve as is well known in the art (see col. 4 lines 34-44). Various buffers and means for adjusting pH may be used as long as the resulting preparation is ophthalmically acceptable. Benzalkonium choride may be used as a preservative. Burke does not disclose the preservative to be a chlorite component.

Beck discloses compositions including a liquid medium, a cylodextrin component and a preservative component which has a reduced tendency of being complexed with the cyclodextrin component. In one embodiment, the preservative component is a chlorite component. Active compounds, such as pharmaceutically active components or drugs, preferably are included in the compositions (see abstracts). For example, the present compositions may include a pharmaceutically effective in providing a therapeutic effect when administered to the eyes of a human or animal. The preservative employed is preferably ophthalmically acceptable at the concentration employed so that the human or animal is effectively treated without significant harm caused by the presence of the preservative (see col. 1). Preferably, the preservative component has in increased or greater preservative efficacy in the composition relative to an identical amount (w/v) of benzalkonium chloride.

Absent unexpected results, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the composition of Burke by substituting the preservative, chlorite as taught by Beck for the benzalkonium choride because of the expectation of increased or greater preservative efficacy as taught by Beck.

***Correspondence***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Rachel M. Bennett whose telephone number is (703) 308-8779. The examiner can normally be reached on Monday through Friday, 8:00 A.M. to 4:30 P.M..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman K. Page can be reached on (703) 308-2927. The fax phone numbers for the

organization where this application or proceeding is assigned are (703) 305-3592 for regular communications and (703) 308-7924 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1234.

R. Bennett
December 10, 2002

CARLOS AZPURU
PRIMARY EXAMINER
GROUP 1500

| Notice of References Cited | Application/Control No. 10/236,566 | Applicant(s)/Patent Under Reexamination OLEJNIK ET AL. | |
|---|---|---|---|
| | Examiner Rachel M. Bennett | Art Unit 1615 | Page 1 of 1 |

**U.S. PATENT DOCUMENTS**

| * | | Document Number Country Code-Number-Kind Code | Date MM-YYYY | Name | Classification |
|---|---|---|---|---|---|
| | A | US-US006358935B1 | 03-2002 | Beck et al. | 514/58 |
| | B | US-US005215991A | 06-1993 | Burke | 514/255 |
| | C | US-US 20020071874A1 | 06-2002 | Olejnik et al. | 424/661 |
| | D | US-US 2002/0032201A1 | 03-2002 | Olejnik et al. | 514/249 |
| | 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.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 10/236,566 | 09/06/2002 | Orest Olejnik | D-2892CON | 3779 |

33197 7590 03/03/2003

STOUT, UXA, BUYAN & MULLINS LLP
4 VENTURE, SUITE 300
IRVINE, CA 92618

| EXAMINER | |
|---|---|
| BENNETT, RACHEL M | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1615 | 5 |

DATE MAILED: 03/03/2003

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

PTO-90C (Rev. 07-01)

| Interview Summary | Application No. 10/236,566 | Applicant(s) OLEJNIK ET AL. | |
|---|---|---|---|
| | Examiner Rachel M. Bennett | Art Unit 1615 | |

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

(1) *Rachel M. Bennett*. (3)_____.

(2) *Carlos A. Fisher*. (4)_____.

Date of Interview: *25 February 2003* .

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: *all pending claims* .

Identification of prior art discussed: *Burke (US 5215991)* .

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

Substance of Interview including description of the general nature of what was agreed to if an agreement was reached, or any other comments: *The attorney explained the advantages of the composition comprising up to about 0.15%(w/v) of 5-bromo-6-(2-imidozolin-2-ylamino) quinozaline tartate, wherein the composition has a pH of about 7.0 or greater were unexpected. The attorney agreed to file a declaration showing the unexpected results. Furthermore, the attorney agreed to file a Terminal Disclaimer when allowable subject matter is indicated in the instant application*

(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.)

i)☐ It is not necessary for applicant to provide a separate record of the substance of the interview(if box is checked).

Unless the paragraph above has been checked, 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 ONE MONTH FROM THIS INTERVIEW DATE TO FILE A STATEMENT OF THE SUBSTANCE OF THE INTERVIEW. See Summary of Record of Interview requirements on reverse side or on attached sheet.

Rachel Bennett

Examiner's signature, if required

Examiner Note: You must sign this form unless it is an Attachment to a signed Office action.

U.S. Patent and Trademark Office
PTO-413 (Rev. 03- 98) Interview Summary Paper No. 5.

## 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 unless both applicant and examiner agree that the examiner will record same. Where the examiner agrees to record the substance of the interview, or when it is adequately recorded on the Form or in an attachment to the Form, the examiner should check the appropriate box at the bottom of the Form which informs the applicant that the submission of a separate record of the substance of the interview as a supplement to the Form is not required.

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.

**DRAFT CLAIMS: FOR DISCUSSION PURPOSES ONLY**
SERIAL NO. 10/236,566
GROUP ART UNIT 1615 EXAMINER BENNETT

47. (Amended) A therapeutically effective aqueous ophthalmic composition comprising:
~~water; and~~
up to about 0.15% (w/v) of 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline tartrate, the composition having a pH of about 7.0 or greater, and the 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline tartrate being soluble in the composition at 21°C.

48-52 Original Claims

53. (Amended) The composition of claim 47 which further comprises a preservative selected from the group consisting of an oxy-chloro component and a quaternary ammonium compound in an amount effective to at least assist in preserving the composition.

54-56 Original Claims

57. (Amended) A therapeutically effective aqueous ophthalmic composition comprising:
~~water; and~~
up to about 0.15% (w/v) of a component selected from the group consisting of 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline, salts of 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline, esters of 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline and mixtures thereof, the composition having a pH of about 7.0 or greater, and the component being soluble in the composition at 21°C.

58-66 Original Claims

67. (New) The composition of claim 53 in which the preservative comprises BAK.

68. (New) The composition of claim 57 which further comprises a preservative selected from the group consisting of an oxy-chloro component and a quaternary ammonium compound in an amount effective to at least assist in preserving the composition.

69. (New) The composition of claim 68 in which the preservative comprises BAK.

70. (New) The composition of claim 68 inm ,which the preservative comprises a oxy-chloro component.

DRAFT CLAIMS
DO NOT
ENTER

Received from <+17142464249> at 2/24/03 8:28:58 PM [Eastern Standard Time]

Feb-24-03 08:28pm From-ALLERGAN LEGAL DEPARTMENT +17142484249 T-976 P.01/07 F-220

# FACSIMILE TRANSMISSION

**FROM:** Carlos A. Fisher
ALLERGAN, Inc.
P.O. Box 19534
2525 Dupont Drive
Irvine, CA 92623-9534

Phone No.: 714-246-4920
Facsimile No.: 714-246-4249

**TO:** The United States Patent and Trademark Office
Assignment Division, Attention: Examiner Rachael Bennett
Facsimile No.: 703-746-5315

Number of pages (including this cover page): 7

*Please acknowledge receipt of all pages indicated above by faxing this page back to Allergan, Inc at the facsimile number provided above*

In re Application of: Olejink et al.

Serial No.: 09/904,018 and 10/236,566

Examiner: Rachael Bennett

Date: February 24, 2003

Examiner Bennett,

Cotransmitted please find two sets of draft claims for discussion during our telephonic interview; one each for the two above referenced patent applications. I look forward to speaking with you at 8:30 PST.

Best wishes,

Carlos Fisher
Reg. 36, 510

Received from <+17142484249> at 2/24/03 8:28:58 PM [Eastern Standard Time]

OIPE JC48 MAR 24 2003 PATENT & TRADEMARK OFFICE

#68
RECEIVED 4/2/03
MAR 28 2003
TECH CENTER 1600/2900

DOCKET NO: 4361CON(AP) PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of Olejnik, et al.

Serial No: 10/236,566

Filed: September 6, 2002

For: COMPOSITIONS CONTAINING ALPHA-2-ADRNERGIC AGONIST COMPONENTS

Group Art Unit: 1615

Examiner: Bennett, R.

## REPLY TO OFFICE ACTION

This communication is in Reply to the Office Action mailed December 18, 2001. Applicants have carefully studied the Office Action, and respectfully request reconsideration of the claim rejections in light of the claim amendments and comments which follow.

03/27/2003 CVD111 00000051 010885 10236566
01 FC:1202 72.00 CH

## AMENDMENTS TO THE CLAIMS

Kindly make the following amendments to the claims:

47. (Amended) A therapeutically effective aqueous ophthalmic composition comprising:
~~water; and~~
up to about 0.15% (w/v) of 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline tartrate, the composition having a pH of about 7.0 or greater, and the 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline tartrate being soluble in the composition at about 21°C.

48-52 Original Claims

55. (Amended) The composition of claim 47 which further comprises a preservative selected from the group consisting of an oxy-chloro component and a quaternary ammonium compound in an amount effective to at least assist in preserving the composition.

54-56 Original Claims

57. (Amended) A therapeutically effective aqueous ophthalmic composition comprising:
~~water; and~~
up to about 0.15% (w/v) of a component selected from the group consisting of 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline, salts of 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline, esters of 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline and mixtures thereof, the composition having a pH of about 7.0 or greater, and the component being soluble in the composition at about 21°C.

58-66 Original Claims

67. (New) The composition of claim 55 in which the preservative comprises benzalkonium chloride.

68. (New) The composition of claim 57 which further comprises a preservative selected from the group consisting of an oxy-chloro component and a quaternary ammonium compound in an amount effective to at least assist in preserving the composition.

69. (New) The composition of claim 68 in which the preservative comprises benzalkonium chloride.

70. (New) The composition of claim 68 in, which the preservative comprises a oxy-chloro component.

## REMARKS

Applicants would like to thank Examiner Bennett for her courtesy in granting and conducting a telephonic interview on February 25, 2003. During the interview Examiner Bennett and the undersigned discussed the outstanding rejections and proposed claim amendments.

Independent claims 47 and 57 and dependent claim 53 have been amended, and new claims 67-70 added. All the amendments are supported by the specification. Claims 47 and 57 were amended to indicate that what is being claimed is a therapeutically effective aqueous ophthalmic composition. Support for this amendment can be found, e.g., at page 1, lines 15-16 and page3-7. Claim 52 was amended to add a Markush group of preservative components including oxy-chloro compounds and quaternary ammonium compounds; see pages 18-20. The new claims provide specific embodiments of the invention.

Applicants would like to point out that these claim amendments and cancellations have been made solely in order to enable early allowance of certain aspects of the invention; Applicants have amended claims in this application with the understanding that they may reserve the right to present the unamended versions thereof in a subsequent patent application.

*Provisional Double Patenting*

The Examiner has made a provisional double patenting rejection of the invention claimed in this patent application over co-pending patent application Serial No. 09/904,018. Applicants are herewith filing a Terminal Disclaimer over the '018 application; thus Applicant believe this rejection is now moot

*35 USC §103*

The Examiner rejected claims 47-66 as being unpatentable pursuant to 35 USC §103 over Burke (US 5,215,991). Although not explicitly stated, Applicants infer that this rejection is in view of Beck (US Patent 6,358,935), since the discussion mentions the Beck patent. If Applicants are in error, correction is respectfully sought. The Examiner has stated that Burke discloses brimonidine (5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline) in various formulations and concentrations, including an aqueous formulation; the Examiner also states that Beck discloses cyclodextrin-containing compositions containing an oxy-chloro component. The Examiner argues that the currently claimed invention is the result of routine optimization of the conditions cited in Burke. Moreover, the Examiner has cited Beck for the disclosure of oxy-chloro preservatives therein, notwithstanding these preservatives are disclosed as for use with cyclodextrins, which not elements of the compositions presently claimed. Applicants respectfully traverse this rejection for the following reasons.

The current claims are directed to therapeutically effective aqueous ophthalmic compositions comprising brimonidine and salts and esters thereof at a pH of up to about 7.0, and in a concentration of about 0.15% or less. Other claims indicate that the composition is preserved using a quaternary ammonium preservative or an oxychloro preservative.

To appreciate the surprising aspects of the present invention it is important to understand that previous brimonidine solutions for ophthalmic use have been formulated at a pH of about 6.3 – 6.5 and a concentration of 0.2% (w/v). This formulation was approved for marketing in the United States and foreign countries under the trade name Alphagan®.

The present invention is the result of the surprising finding that increasing the pH of a brimonidine solution to a pH of greater than about 7.0 leads to similar efficacy at a 25% lower concentration (from 0.2% (w/v) to about 0.15% (w/v) or less) than is seen in a brimonidine solution at a pH of about 6.6-6.8. This appears to be due to the fact that at a pH closer to the pKa of brimonidine (which has a pKa of about 7.4) than pH 6.3-6.5, a larger proportion of the molecules are electrostatically neutral, and thus less lipophobic than the polarized molecule. As such, a greater amount of the active drug is able to enter the cornea of the eye at a given solution concentration; this effect counters the effects of decreased brimonidine solubility at the higher pH. See specification at e.g., paragraph bridging pages 1 and 2.

However, it is particularly surprising that such a therapeutically effective dosage of brimonidine could be formulated in aqueous solution at a pH greater than about 7.0. Figure 1 of the present specification shows that brimonidine's solubility decreases precipitously at pH values above 7.0. The fact that a therapeutically effective dosage could be provided by a composition containing about 0.15% or less of brimonidine at such pH values is truly unexpected.

For the Examiner's convenience, Applicants hereby attach a copy of an article Katz, et al., *J. Glaucoma* 11:119 (April 2002) which shows the comparison of the 0.2% brimonidine formulation having a pH 6.3-6.5 (the "0.2% formulation") with 0.15% brimonidine solution at pH 7.2 (the 0.15% formulation).

Although the Katz paper does not disclose the pH of either solution, Applicants hereby enclose a Declaration of Amy Batoosingh, Director of Ophthalmological Clinical Research at Allergan, Inc. Ms. Batoosingh, whose work is contained within and acknowledged on page 126 of Katz, indicates in her Declaration that the formulation called "brimonidine 0.2%" in the Katz paper, which used benzalkonium chloride as a preservative, comprised 0.2% brimonidine at pH 6.3-6.5, and that the formulation termed "brimonidine-Purite 0.15%" in Katz, (which used oxy-chloro as a preservative) comprised 0.15% brimonidine at pH 7.2.

As can be seen in Figure 1 on page 122 of Katz, topical application of the 0.15% formulation resulted in no statistically significant differences in its ability to lower intraocular pressure (IOP) compared to the 0.2% formulation, despite 25% less active agent in the former formulation. Thus,