EXHIBIT F , TAB 4

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
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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.

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4a) Of the above claim(s) _____ is/are withdrawn from consideration.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

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)quinoaxaline. 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-US00635893581	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.

EXHIBIT F , TAB 5



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
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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.

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

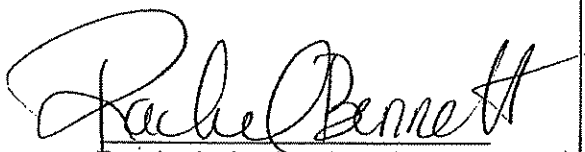
Agreement with respect to the claims f)☒ somewhat was reached. g)☐ was not reached. h)☐ N/A.

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.



Examiner's signature, if required

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

Summary of Record of Interview Requirements

Manual of Patent Examining Procedure (MPEP), Section 713.04, Substance of Interview Must be Made of Record
A complete written statement as to the substance of any face-to-face, video conference, or telephone interview with regard to an application must be made of record in the application whether or not an agreement with the examiner was reached at the interview.

Title 37 Code of Federal Regulations (CFR) § 1.133 Interviews
Paragraph (b)
In every instance where reconsideration is requested in view of an interview with an examiner, a complete written statement of the reasons presented at the interview as warranting favorable action must be filed by the applicant. An interview does not remove the necessity for reply to Office action as specified in §§ 1.111, 1.135. (35 U.S.C. 132)

37 CFR §1.2 Business to be transacted in writing.
All business with the Patent or Trademark Office should be transacted in writing. The personal attendance of applicants or their attorneys or agents at the Patent and Trademark Office is unnecessary. The action of the Patent and Trademark Office will be based exclusively on the written record in the Office. No attention will be paid to any alleged oral promise, stipulation, or understanding in relation to which there is disagreement or doubt.

The action of the Patent and Trademark Office cannot be based exclusively on the written record in the Office if that record is itself incomplete through the failure to record the substance of interviews.

It is the responsibility of the applicant or the attorney or agent to make the substance of an interview of record in the application file, unless the examiner indicates he or she will do so. It is the examiner's responsibility to see that such a record is made and to correct material inaccuracies which bear directly on the question of patentability.

Examiners must complete an Interview Summary Form for each interview held where a matter of substance has been discussed during the interview by checking the appropriate boxes and filling in the blanks. Discussions regarding only procedural matters, directed solely to restriction requirements for which interview recordation is otherwise provided for in Section 812.01 of the Manual of Patent Examining Procedure, or pointing out typographical errors or unreadable script in Office actions or the like, are excluded from the interview recordation procedures below. Where the substance of an interview is completely recorded in an Examiners Amendment, no separate Interview Summary Record is required.

The Interview Summary Form shall be given an appropriate Paper No., placed in the right hand portion of the file, and listed on the "Contents" section of the file wrapper. In a personal interview, a duplicate of the Form is given to the applicant (or attorney or agent) at the conclusion of the interview. In the case of a telephone or video-conference interview, the copy is mailed to the applicant's correspondence address either with or prior to the next official communication. If additional correspondence from the examiner is not likely before an allowance or if other circumstances dictate, the Form should be mailed promptly after the interview rather than with the next official communication.

The Form provides for recordation of the following information:
- Application Number (Series Code and Serial Number)
- Name of applicant
- Name of examiner
- Date of interview
- Type of interview (telephonic, video-conference, or personal)
- Name of participant(s) (applicant, attorney or agent, examiner, other PTO personnel, etc.)
- An indication whether or not an exhibit was shown or a demonstration conducted
- An identification of the specific prior art discussed
- An indication whether an agreement was reached and if so, a description of the general nature of the agreement (may be by attachment of a copy of amendments or claims agreed as being allowable). Note: Agreement as to allowability is tentative and does not restrict further action by the examiner to the contrary.
- The signature of the examiner who conducted the interview (if Form is not an attachment to a signed Office action)

It is desirable that the examiner orally remind the applicant of his or her obligation to record the substance of the interview of each case 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.

Feb-24-03 06:20pm From-ALLERGAN-LEGAL DEPARTMENT +17142464249 T-376 P.03/07 F-220

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 compositon 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 +17142464249 T-376 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.: 09804,018 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 tele[phonic 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 < +17142464249 > at 2/24/03 8:28:58 PM [Eastern Standard Time]

EXHIBIT F , TAB 6

OIPE JC48
MAR 2 4 2003
PATENT & TRADEMARK OFFICE

RECEIVED
MAR 2 8 2003
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#6B
4/2/03

DOCKET NO. 4361CON (A)
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 CVO111 00000051 010885 10236566
01 FC:1202 72.00 CH

AMENDMENTS TO THE CLAIMS

Kindly make the following amendments to the claims:

1 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

6 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

10 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

19 67. (New) The composition of claim 6 55 in which the preservative comprises benzalkonium chloride.

20 68. (New) The composition of claim 16 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.

21 69. (New) The composition of claim 20 68 in which the preservative comprises benzalkonium chloride.

22 70. (New) The composition of claim 20 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,

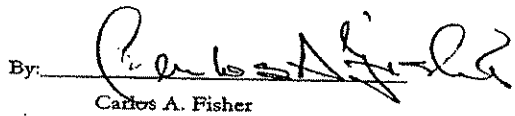
lowering the concentration, when the pH is above about 7.0 unexpectedly had no significant effect on therapeutic efficacy, when compared to the 0.2% formulation.

The advantages of this invention are manifest. Among others, it can be seen that although ophthalmic hypotensive therapeutic efficacy of the 0.15% solution is the same as for the 0.2% solution, the reduced concentration (and thus the reduced dosage) results in a lower potential for systemic side effects, which are typically caused by drainage of topically applied drugs from the eye to the stomach through the nasolacrimal duct. Although brimonidine's side effects are not as severe as some other glaucoma medications, they can still include sedation, hypotension, and reduction in heat rate in some patients. A reduction in the dosage by 25% reduces the likelihood and severity of such side-effects.

Thus, the present invention is drawn to surprising new therapeutic compositions comprising at least a 25% lower concentration of brimonidine than previous ophthalmic formulations, at pH closer both to the solubility limits of brimonidine, and to the pKa of the compound.

For this reason it can be seen that these results were completely unforeseen and surprising, and could therefore not have been anticipated by a person of skill in the art. For this reason, Applicants respectfully request reconsideration and withdrawal of the outstanding rejection, and ask the Examiner to permit the claims to proceed to issue. Should there be any fee in connection with this communication, the Director is authorized to use the Applicants' Deposit Account 01-0885 for the payment of such fees.

Respectfully submitted,

By: 

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DOCKET NO. 17361CON(AP)
PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of Olejnik, et al.

Serial No: 10/236,566
Conf. No.: 3779
Filed: September 6, 2002

For: COMPOSITIONS CONTAINING ALPHA-2-ADRENERGIC AGONIST COMPONENTS

Group Art Unit: 1626

Examiner: Bennett, R.

TRANSMITTAL SHEET

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

Transmitted herewith is an Amendment in the above-identified application. Enclosed are:

1) Return/Stamped Postcard
2) Transmittal Sheet
3) Reply and Amendment (5 pgs.)
4) Terminal Disclaimer
5) Declaration of Amy Batoosingh, B.A.

CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Box Amendment-Fee; Assistant Commissioner for Patents, Washington, D.C. 20231 on

3/17/2003 (Date of Deposit)

BONNIE FERGUSON Name of person mailing correspondence

3/17/2003 Date of Signature

Bonnie Ferguson Signature

Serial No. 10/236,560 2 Docket No. 17361CON(AP)

The fee has been calculated as shown below:

CLAIMS AS FILED

	CLAIMS REMAINING AFTER AMENDMENT	HIGHEST NO. PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE	FEE
Total Claims	24	20	= 4 ×	$18	= $72.00
Independent Claims	2	2	= 0 ×	$84	= $0.00
If application has been amended to contain multiple dependent claim(s), then add			No	$280	= $0.00
(Select only one)					
Time Extension Fees:			one month	$110	= $
			two months	$410	= $
			three months	$930	= $
			four months	$1,450	= $
			TOTAL ADDITIONAL FEE FOR THIS AMENDMENT		$72.00

( ) A check in the amount of $* is enclosed (place fee in here i.e., petition, excess claims, etc.)

(x) The Commissioner is hereby authorized to charge fees under 37 CFR 1.16 and 1.17 (associated with petition fees or excess claim fees) which may be required, or credit any overpayment to Deposit Account No. 01-0885. A duplicate copy of this sheet is enclosed.

Respectfully Submitted,

Date: 3/17/05

Signature: Carlos A. Fisher

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62

EXHIBIT F , TAB 7

OIPE JC48 MAR 24 2003 PATENT & TRADEMARK OFFICE

RECEIVED MAR 28 2003 TECH CENTER 1600/2900

DOCKET NO. 17361CON1APP
PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of Olejnik, et al.	Group Art Unit: 1626
Serial No: 10/236,566	Examiner: Bennett, R.
Filed: September 6, 2002	
For: COMPOSITIONS CONTAINING ALPHA-2-ADRNERGIC AGONIST COMPONENTS	

rb 4-10-03

DECLARATION OF AMY BATOOSINGH

Dear Sir,

I, Amy Batoosingh, B.A., hereby declare as follows:

1. I hold the title of Director, Ophthalmological Clinical Research at Allergan, Inc. I have worked in the Department of Clinical Research at Allergan for over 20 years.

2. I am a co-author of the article, Katz, et al., *J. Glaucoma* 11:119 (April 2002), entitled *Twelve-Month Evaluation of Brimonidine Purite Versus Brimonidine in Patients with Glaucoma or Ocular Hypertension,* and am familiar with the studies referenced therein.

3. The compositions called "brimonidine 0.2%" and "brimonidine-Purite 0.15%" in the Katz article comprised 0.2% (w/v) brimonidine at pH 6.3-6.5, and 0.15% brimonidine at pH 7.1-7.3, respectively.

4. The conclusion reached as a result of the studies referenced in the Katz et al., article was that brimonidine 0.2% and brimonidine-Purite 0.15% showed comparable efficacy when each was used for the treatment of ocular hypertension in glaucoma and/or ocular hypertensive human patients over a 12 month period of time, despite a significant reduction in the concentration of the active ingredient in the latter formulation.

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

Sincerely yours,

Amy Batoosingh, B.A.

J Glaucoma 2002
Apr;11(2):119-126

2002050756

Twelve-Month Evaluation of Brimonidine-Purite Versus Brimonidine in Patients With Glaucoma or Ocular Hypertension

L. Jay Katz, MD

Brimonidine-Purite Study Groups 1 and 2, Wills Eye Hospital, Philadelphia, Pennsylvania

Purpose: To compare the efficacy and safety of brimonidine-Purite (Alphagan; Allergan, Irvine, CA) 0.15% and 0.2% three times daily with brimonidine (Alphagan) 0.2% three times daily in patients with glaucoma or ocular hypertension.

Patients and Methods: In this 12-month, randomized, multicenter, double-masked, parallel-group study, patients were randomly assigned to receive brimonidine-Purite 0.15% (n = 381), brimonidine-Purite 0.2% (n = 383), or brimonidine 0.2% (n = 383) three times daily. Visits were conducted before the study, at baseline, at weeks 2 and 6, and at months 3, 6, 9, and 12. Diurnal intraocular pressure was measured at 8 AM, 10 AM, 3 PM, and 5 PM at baseline, week 6, and at months 3, 6, and 12. Intraocular pressure was also measured at 8 and 10 AM at week 2 and month 9. Safety was evaluated by adverse events and other ocular and systemic measures.

Results: At baseline, mean intraocular pressure was similar in the three treatment groups. During follow-up, there were no statistically significant among-group differences in mean intraocular pressure or mean changes from baseline intraocular pressure (at peak or trough). The difference in mean intraocular pressure between the brimonidine-Purite-0.15% and brimonidine-0.2% treatment group was less than 1 mm Hg at all time points. The relative percent difference in allergic conjunctivitis was 41% lower in the brimonidine-Purite 0.15% group compared with the brimonidine 0.2% group. The comfort and satisfaction rating significantly favored brimonidine-Purite 0.15%.

Conclusions: Over 12-months, brimonidine-Purite 0.15% and 0.2% provided intraocular pressure lowering comparable with brimonidine 0.2% in patients with glaucoma or ocular hypertension. Brimonidine-Purite 0.15% showed the most favorable safety and tolerability profile with a reduced incidence of allergic conjunctivitis and better satisfaction and comfort rating.

Key Words: Benzalkonium chloride—Brimonidine—Glaucoma—Ocular hypertension—Purite.

Since the introduction of brimonidine 0.2% ophthalmic solution (Alphagan; Allergan, Irvine, CA) in 1996, this highly selective α_2-adrenergic agonist has proven to be an effective and safe agent for the long-term management of glaucoma and ocular hypertension.[1] In a randomized, continuous clinical trial, the efficacy of brimonidine 0.2% twice daily was sustained over 4 years and was comparable with the efficacy of timolol 0.5%.[2–6] Additional studies have shown the flexibility of brimonidine 0.2% twice daily as an effective monotherapy, adjunctive, and replacement therapy.[7–9] Brimonidine 0.2% twice daily has become a widely accepted first- and second-line therapy for the long-term management of glaucoma and ocular hypertension.

Studies show that brimonidine 0.2% has a lower risk of systemic adverse events than topical β-blockers.[2,3,7,10,11] In addition, brimonidine 0.2% has a lower

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Members of the Brimonidine-Purite Study Groups 1 and 2 are listed in the Appendix at the end of this article.
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incidence of ocular allergy and shows no cross toxicity compared with apraclonidine (Iopidine; Alcon, Fort Worth, TX).[12] Reports of ocular allergy associated with chronic brimonidine therapy range from 4.2% to 12.7% of patients, depending on the diagnostic criteria and duration of therapy.[1,4,13]

A new formulation of brimonidine ophthalmic solution has been developed to enhance safety and tolerability while maintaining effective intraocular pressure (IOP) reduction. Brimonidine-Purite (Alphagan, Allergan, Irvine, CA) has a different preservative and a lower concentration of active drug than the original brimonidine 0.2% (Alphagan). In the reformulation, the preservative has been changed from benzalkonium chloride (BAK) to Purite. Benzalkonium chloride is the most common antimicrobial preservative used in topical multiuse ophthalmic preparations, including most glaucoma medications.[14,15] It works by denaturing proteins, lysing cytoplasmic membranes, and oxidizing enzymes. At high concentrations, BAK may be more toxic than other preservatives. It can accumulate and remain in ocular tissue for relatively lengthy periods, and may induce cell death in a dose-dependent manner.[16,17] Because glaucoma is a chronic disease and patients may be taking multiple glaucoma medications, these patients may be exposed to high concentrations of BAK with potentially detrimental ocular effects. In contrast, Purite is a stabilized oxychloro complex and oxidative preservative used in Refresh Tears (Allergan, Irvine, CA) artificial eye lubricant and Lens Plus Purite (Allergan, Irvine, CA) Saline.[18–20] When Purite is exposed to light, it is converted to natural tear components (i.e., sodium and chloride ions, oxygen, and water).[21] Purite is a microbicide with a wide spectrum of antimicrobial activity and a very low level of toxicity in mammalian cells.[22]

In addition to the change in preservative, brimonidine-Purite 0.15% contains 25% less active drug than original brimonidine 0.2%. Animal studies suggest that brimonidine tartrate has enhanced ocular bioavailability when formulated as brimonidine-Purite.[23] In addition, 0.15% is the lowest effective concentration tested, which attains the desired therapeutic effect.[24] Therefore, the new formulation of brimonidine may provide an improved safety and tolerability profile with comparable efficacy.

The objective of this study was to evaluate the safety and efficacy of brimonidine-Purite 0.15% and 0.2% compared with brimonidine 0.2%. The results represent the pooled analyses of two identically designed clinical trials. All three study medications were administered three times daily for 1 year in patients with glaucoma or ocular hypertension. Although brimonidine twice daily has been shown to be as effective as three-times-daily brimonidine,[24,25] the three-times-a-day dosage was selected for this study to satisfy US regulatory requirements.

PATIENTS AND METHODS

Study Design

Two identically designed, 12-month, double-masked, randomized, parallel-group studies were conducted at 44 sites across the United States. The results presented here are from the analyses of pooled data from these two clinical trials. The studies were conducted in accordance with Institutional Review Board and Informed Consent Regulations. Each investigator obtained appropriate review board approval before study initiation. All patients gave their written consent before participating in any study-related activities. Patients who were treated with ocular hypotensive medications before study entry were required to undergo a washout period ranging from 4 to 28 days, depending on the medication taken. This washout eliminated any potential residual effects of previous therapy.

Patients were randomly assigned to receive brimonidine-Purite 0.15% (n = 381), brimonidine-Purite 0.2% (n = 383), brimonidine 0.2% (n = 383) three times daily in the morning (7:30–8:30 AM), in the mid-afternoon (2:30–3:30 PM), and in the evening (9:30–10:30 PM). Scheduled visits occurred before study, at baseline, at weeks 2 and 6, and at months 3, 6, 9, and 12.

Criteria

Key inclusion criteria included an age of 18 years or older with a diagnosis of glaucoma (primary open angle, pseudoexfoliative, pigment dispersion, chronic angle closure with a patent peripheral iridectomy/iridotomy for at least 3 months) or ocular hypertension (IOP $\geq$ 22 mm Hg, $\leq$ 34 mm Hg in each eye after washout, with between-eye IOP asymmetry $\leq$ 5 mm Hg), likelihood to be controlled on monotherapy, negative pregnancy test for women of childbearing potential, and best corrected visual acuity of 20/100 or better.

Key exclusion criteria included uncontrolled systemic disease, other active ocular disease, abnormally low or high blood pressure or heart rate, anticipated alteration of existing chronic therapy with agents that could substantially affect IOP, use of ocular medication other than periodic use of artificial tears, and functionally significant visual field loss.