DETAILED ACTION

The examiner acknowledges receipt of Supplemental Information Disclosure Statement filed 9/23/02.

Election/Restrictions

1. Applicant's election with traverse of Group I in Paper No. 6 is acknowledged. The traversal is on the ground(s) that each of the present claims 1 to 46 involve an alpha-2-adrenergic agonist component and/or a quinoxaline component and therefore, each of the present claims is closely related. This is not found persuasive because while the claims are related, they are patentably distinct.

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

Double Patenting

2. 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).

Claims 24-30 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 47-52, 57-62 of copending Application No. 10/236566. 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 while Application 10/236566 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.

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

Specification

Claim Rejections - 35 USC § 112

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

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

4. Claims 1,7-8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 7-8 are indefinite because Applicants do not clearly define "substantially unionized". Clarification is request.

Claim Rejections - 35 USC § 103

5. 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.

6. Claims 1-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Burke (US 5215991) and in further view of Remington's Pharmaceutical Sciences.

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. Burke does not disclose the solubility enhancing agent to be carboxymethylcellulose or the pH of the composition.

Remington discloses carboxymethylcellulose sodium as a known pharmaceutic aid for use as a suspending agent or viscosity-increasing agent (see page 1305).

Absent unexpected results, it is the position of the examiner 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 adding carboxymethylcellulose in order to achieve the desired viscosity as taught by Remington. Burke teaches topical ophthalmic preparations, for example ocular drops, gels or creams, are preferred because of ease of application, ease of dose delivery and fewer systemic side effects. Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to add a suitable amount of

carboxymethylcellulose to achieve the desired viscosity in order to ease the application, as taught by Burke. Furthermore, Burke desires the formulation to ophthalmically acceptable. Thus, one of ordinary skill in the art would determine a pH that is suitable for a composition, which is administration into the eye.

7. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. See PTO-892.

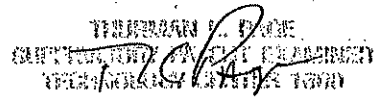
Correspondence

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
January 9, 2003



Notice of References Cited	Application/Control No. 09/904,018	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-US005215991A	06-1993	Burke	514/255
*	B	US-US005459133A	10-1995	Neufeld	514/211
	C	US-US 20020071874A1	06-2002	Olejnik et al.	424/661
	D	US-US 20020010202 A1	01-2002	Garst	514/392
	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	Remington's Pharmaceutical Sciences, Eighteenth Edition, 1990, pages 1304-1305.
	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 D , TAB 8

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.
09/904,018	07/10/2001	Orest Olejnik	D-2892	1779

7590 03/03/2003

Frank J. Uxa
Stout, Uxa, Buyan & Mullins, LLP
Suite 300
4 Venture
Irvine, CA 92618

EXAMINER	
BENNETT, RACHEL M	

ART UNIT	PAPER NUMBER
1615	

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)	
	09/904,018	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 instant invention was an invention of selection. The attorney agreed to file a declaration showing unexpected results with regards to the anionic solubility enhancing agent. The attorney also indicated support for "substantially unionized" is found on pages 1-2 of the specification. It was agreed upon that a terminal disclaimer would be filed when allowable subject matter was 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.

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. 09/904,018, Our Docket 17361
Group Art Unit 1615 Examiner BENNETT

1. (Amended) A therapeutically effective aqueous composition comprising:

~~an alpha-2-adrenergic agonist component~~ a therapeutically active component selected from the group consisting of 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline, a salt thereof, and an ester thereof in an amount effective to provide a therapeutic benefit to a patient to whom the composition is administered; and

an anionic solubility enhancing component in an amount effective to increase the solubility of the alpha-2-adrenergic agonist component in the composition relative to the solubility of an identical alpha-2-adrenergic agonist component in a similar composition without the solubility enhancing component; ~~and~~

~~a liquid carrier component.~~

2. Cancel

3. Cancel

4. Cancel

5. Cancel

6. Original claim

7. Original claim

8. Original claim

9. (Amended) The composition of claim 1 wherein the ~~therapeutically active alpha-2-adrenergic agonist~~ component has increased diffusion through a lipid membrane relative to an identical therapeutically active ~~alpha-2-adrenergic agonist~~ component in a similar composition without the solubility enhancing component.

10. Cancel

11. Original claim

12. Cancel

13. (Amended) The composition of claim ~~12~~ 1 wherein said polyanionic component is selected from the group consisting of anionic cellulose derivatives, anionic polymers derived from acrylic acid, anionic polymers derived from

DRAFT claims
DO NOT ENTER

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

DRAFT CLAIMS: FOR DISCUSSION PURPOSES ONLY
Serial No. 09/904,018, Our Docket 17361
Group Art Unit 1615 Examiner BENNETT

methacrylic acid, anionic polymers derived from alginic acid, anionic polymers derived from amino acids and mixtures thereof.

14. Original claim.

15. Original claim.

16. Original claim.

17. Original claim.

18. Original claim.

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

Feb-24-03 08:30pm From-ALLERGAN LEGAL DEPARTMENT +17142464249 T-976 P.08/07 F-220

DRAFT CLAIMS, FOR DISCUSSION PURPOSES ONLY
Serial No. 09/904,018, Our Docket 17361
Group Art Unit 1615 Examiner BENNETT

19. Cancel

20. Cancel

21. Original claim.

22. Original claim.

23. Original claim.

24. (Amended) A therapeutically effective aqueous composition comprising:

a therapeutically active component selected from the group consisting of 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline, a salt thereof, and an ester thereof ~~an alpha-2-adrenergic agonist component~~ in an amount effective to provide a therapeutic benefit to a patient to whom the composition is administered; and

an anionic cellulose derivative in an amount effective to increase the solubility of the alpha-2-adrenergic agonist component; ~~and~~

~~an aqueous liquid carrier component.~~

25. Original claim

26. Original claim.

27. Original claim

28. (Amended) A therapeutically effective aqueous composition comprising:

a tartrate of 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline in an amount effective to provide a therapeutic benefit to a patient to whom the composition is administered; and

an anionic solubility enhancing component in an amount effective to increase the solubility of the tartrate of 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline; ~~and~~

~~an aqueous liquid carrier component.~~

29. Original claim

30. Original claim

47. (New) The composition of claim 1 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.

DRAFT Claims — DO NOT ENTER

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

48. (New) The composition of claim 47 in which the preservative comprises BAK.

49. (New) The composition of claim 47 in which the preservative comprises an oxy-chloro component.

50. (New) The composition of claim 47 in which the preservative comprises a chlorite component.

51. (New) The composition of claim 24 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.

52. (New) The composition of claim 51 in which the preservative comprises BAK.

53. (New) The composition of claim 51 in which the preservative comprises an oxy-chloro component.

54. (New) The composition of claim 51 in which the preservative comprises a chlorite component.

55. New) The composition of claim 24 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.

56. (New) The composition of claim 51 in which the preservative comprises BAK.

57. (New) The composition of claim 51 in which the preservative comprises an oxy-chloro component.

58. (New) The composition of claim 51 in which the preservative comprises a chlorite component.

EXHIBIT D , TAB 9

OIPE JC37
MAR 17 2003
PATENT & TRADEMARK OFFICE

RECEIVED
1615
MAR 19 2003
TECH CENTER 1600/2900

PTO/SB/122 (10-01)
Approved for use through 10/31/2002 OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

CHANGE OF CORRESPONDENCE ADDRESS
Application

Address to:
Commissioner for Patents
Washington, D.C. 20231

Application Number	09/904,018
Filing Date	July 10, 2001
First Named Inventor	Olejnik
Art Unit	1615
Examiner Name	Bennett, R.M.
Attorney Docket No.	D-2892

Please change the Correspondence Address for the above-identified application to:

☐ Customer Number _____ *Customer Number* → _____ *Customer Number Bar Code*

OR

9/ Change of Address

☒ Firm or Individual Name	Carlos A. Fisher				
Address	Allergan, Inc. 2525 Dupont Drive				
City	Irvine	State	CA	Zip	92627
Country	US				
Telephone	714-246-4920	Fax	714-246-4249		

This form cannot be used to change the data associated with a Customer Number. To change the data associated with an existing Customer Number use "Request for Customer Number Data Change" (PTO/SB/124).

I am the:

☐ Applicant/Inventor.

☐ Assignee of record of the entire interest.
Statement under 37 CFR 3.73(b) is enclosed. (Form PTO/SB/96).

☒ Attorney or Agent of record.

☐ Registered practitioner named in the application transmittal letter in an application without an executed oath or declaration. See 37 CFR 1.33(a)(1). Registration Number _____

Typed or Printed Name	Frank J. Uxa
Signature	Frank J. Uxa
Date	March 10, 2003

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below*.

☒ *Total of 1 forms are submitted.

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Commissioner for Patents, Washington, DC 20231, on or before

March 10 2003

Janet McGhee

Title Assist

Date 3/10/03

EXHIBIT D , TAB 10

OIPE JC54
MAR 17 2003
PATENT & TRADEMARK OFFICE

#10/A
Grp
3/25/03

DOCKET NO. 17361 (AR)
PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of Olejnik, et al.

Serial No: 09/904,018

Filed: July 10, 2001

For: COMPOSITIONS CONTAINING ALPHA-2-ADRNERGIC AGONIST COMPONENTS

Group Art Unit: 1626

Examiner: Bennett, R.

RECEIVED
MAR 24 2003
TECH CENTER 1600/2900

REPLY TO OFFICE ACTION

This communication is in Reply to the Office Action mailed January 15, 2003. 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.

AMENDMENTS TO THE CLAIMS

Kindly make the following amendments to the claims:

1. (Currently amended) A therapeutically effective aqueous composition comprising:

~~an alpha-2-adrenergic agonist component~~ a therapeutically active alpha-2-adrenergic agonist component selected from the group consisting of 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline, a salt thereof, and an ester thereof in an amount effective to provide a therapeutic benefit to a patient to whom the composition is administered; and

~~a polyanionic~~ solubility enhancing component in an amount effective to increase the solubility of the alpha-2-adrenergic agonist component in the composition relative to the solubility of an identical alpha-2-adrenergic agonist component in a similar composition without the solubility enhancing component; ~~and~~

~~a liquid carrier component.~~

2. Cancel

3. Cancel

4. Cancel
5. Cancel
6. Original claim

3 7. (Currently amended). The composition of claim 1 wherein the ~~alpha-2-adrenergic agonist~~ therapeutically active component is substantially unionized.

A2

4 8. (Currently amended) The composition of claim 1 wherein the ~~alpha-2-adrenergic agonist~~ therapeutically active component is substantially unionized in a biological environment to which the composition is administered.

5 9. (Currently amended) The composition of claim 1 wherein the therapeutically active ~~alpha-2-adrenergic agonist~~ component has increased diffusion through a lipid membrane relative to an identical therapeutically active ~~alpha-2-adrenergic agonist~~ component in a similar composition without the solubility enhancing component.

10. Cancel

6 11. (Currently amended) The composition of claim 1 wherein the solubility enhancing component is effective to increase the solubility in a biological environment of the ~~alpha-2-adrenergic agonist~~ therapeutically active component relative to the solubility in a biological environment of an identical ~~alpha-2-adrenergic agonist~~ therapeutically active component in a similar composition without the solubility enhancing component.

A3

12. Cancel

7 13. (Currently amended) The composition of claim ~~12~~ 1 wherein said polyanionic component is selected from the group consisting of anionic cellulose derivatives, anionic polymers derived from acrylic acid, anionic polymers derived from methacrylic acid, anionic polymers derived from alginic acid, anionic polymers derived from amino acids and mixtures thereof.

A4

14. Original claim
15. Original claim
16. Original claim
17. Original claim
18. Original claim
19. Cancel
20. Cancel

21. Original claim

22. Original claim

23. Original claim

16 24. (Amended) A therapeutically effective aqueous composition comprising:

A5 a therapeutically active component selected from the group consisting of 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline, a salt thereof, and an ester thereof ~~an alpha-2-adrenergic agonist component~~ in an amount effective to provide a therapeutic benefit to a patient to whom the composition is administered; and

an anionic cellulose derivative in an amount effective to increase the solubility of the therapeutically active ~~alpha-2-adrenergic agonist~~ component; ~~and~~

~~an aqueous liquid carrier component.~~

25. Original claim

26. Original claim

27. Original claim

20 28. (Amended) A therapeutically effective aqueous composition comprising:

A6 a tartrate of 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline in an amount effective to provide a therapeutic benefit to a patient to whom the composition is administered; and

an anionic solubility enhancing component in an amount effective to increase the solubility of the tartrate of 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline; ~~and~~

~~an aqueous liquid carrier component.~~

29. Original claim

30. Original claim

31-46 Withdrawn

23 47. (New) The composition of claim 1 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.

A7

24 ~~48.~~ (New) The composition of claim 23 in which the preservative comprises benzalkonium chloride.

25 ~~49.~~ (New) The composition of claim 23 in which the preservative comprises an oxy-chloro component.

26 ~~50.~~ (New) The composition of claim 23 in which the preservative comprises a chlorite component.

A7 cont

27 ~~51.~~ (New) The composition of claim 16 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.

28 ~~52.~~ (New) The composition of claim 27 in which the preservative comprises benzalkonium chloride.

29 ~~53.~~ (New) The composition of claim 27 in which the preservative comprises an oxy-chloro component.

30 ~~54.~~ (New) The composition of claim 27 in which the preservative comprises a chlorite component.

31 ~~55.~~ New) The composition of claim 20 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.

32 ~~56.~~ (New) The composition of claim 31 in which the preservative comprises benzalkonium chloride.

33 ~~57.~~ (New) The composition of claim 31 in which the preservative comprises an oxy-chloro component.

34 ~~58.~~ (New) The composition of claim 31 in which the preservative comprises a chlorite 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 1, 24 and 28 and dependent claims 7, 8, 9, 11, and 13 have been amended and new claims 47-58 have been added. All the amendments are supported by the specification. For example, claim 1 has been amended to claim a therapeutically effective aqueous composition; this is supported by the specification e.g., at page 20, lines 21-26 and page 21, lines 10-11. The claim has also been amended to indicate that the composition contains 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline or a salt or ester thereof. Support for this amendment is found in, e.g., original claim 4 and the specification at page 10. Finally, claim 1 has been amended to indicate that the solubility enhancing component is a polyanionic component. Support for this amendment can be found at page 4, lines 16-18.

Additionally, claims 2-5,10, 12, 19 and 20 have been cancelled.

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 cancelled and/or amended claims in this application with the understanding that they may present the unamended and non-cancelled 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. 10/236,566. Applicants are herewith filing a Terminal Disclaimer over the '566 application; thus Applicant believe this rejection is now moot

35 USC §112

The Examiner rejected claims 1, 7 and 8 as being indefinite in the use of the language "substantially unionized". Applicants respectfully traverse this rejection.

As an initial matter, this language is only found in claims 7 and 8; thus Applicants believe that claim 1 is not subject to this rejection.

Secondly, the specification at e.g., page 11 lines 13-21 makes clear that in a preferred embodiment of disclosed invention the alpha 2 adrenergic agonist (such as brimonidine (5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline), as now claimed) is substantially unionized (i.e., formulated at a pH approaching or at its pK_a) to facilitate permeation of the compound across membrane lipid bilayers, such as, for example, the cell membranes of corneal cells. In this context, the word "substantially" would be understood by the person of skill in the art to refer to the fact that the alpha agonist is present in the claimed composition as a population of molecules; when substantially unionized at a given pH the majority of the molecules will be electronically neutral, but perhaps not every molecule will be uncharged.

Foe this reason Applicants believe that the term "substantially unionized" is not indefinite, and request reconsideration of the rejection.

35 USC §103

The Examiner has rejected claims 1-30 over Burke (US 5,215,991) in view of Remington Pharmaceutical Sciences. The Examiner has stated that Burke discloses brimonidine in various formulations, including an aqueous formulation; at column 5 it also discloses "vehicles" which could be used in such a formulation; these include polyvinyl alcohol, povidone (polyvinylpyrrolidone), hydroxypropylcellulose, poloxamers, carboxymethylcellulose, hydroxyethylcellulose. Remington is said to teach the desirability of increasing viscosity. Applicants respectfully traverse this rejection for the following reasons.

The current claims are directed to compositions comprising brimonidine and salts and esters thereof in combination with an anionic polymeric solubility enhancing component. The specification (at page 12, lines 13-19) discloses that in preferred embodiments of the invention, the solubility enhancing components are sufficiently anionic to interact with and solubilize the brimonidine.

Of the "vehicles" specifically disclosed by the Burke patent, all will function to increase viscosity of a liquid aqueous composition. However, of these vehicles only carboxymethylcellulose (CMC) is an anionic polymer. All of the other polymers are non-ionic. They may act to increase the solution's viscosity, but they do not have the same characteristics as an anionic polymer such as CMC.

Attached to this communication is a Declaration of Orest Olejnik, Ph.D., Principal Scientist, Pharmaceutical Sciences Department, Allergan Inc. Dr. Graham states in this declaration that anionic solubility enhancing components such as CMC have surprising and beneficial properties in the solubilization of brimonidine as compared to non-ionic or cationic polymers. In particular, the use of an anionic polymer solubility enhancing

component such as CMC (as compared to, for example, hydroxypropyl methyl cellulose) has the advantage of adsorbing to cellular surfaces, such as the cornea of the eye, in a manner that retains any drug in solution with the CMC to be retained at the ocular surface far longer (and in a larger volume) than viscous formulations made with other, non-anionic polymers, while simultaneously increasing solubility.

In light of Dr. Olejnik's Declaration, the patent specification and the state of the art, the Applicants therefore submit that, alone or in combination with Remington, Burke contains no disclosure that would direct or motivate the person of ordinary skill in the art to select or want to select an anionic polymeric solubility enhancing component such as CMC from the list of optional viscous "vehicles" contained in the '991 patent.

Only the present patent application provides the necessary direction; and to pick and choose elements from lists within the prior art to "create" a claimed invention based in whole or in part on the patent application within which it is first disclosed is clearly impermissible hindsight reconstruction of the invention. Yet, the Applicants respectfully believe that this must be the conclusion of the current rejection.

For these reasons, the Applicants respectfully request reconsideration and withdrawal of the pending rejection.

Date: 8/11/03 By: _____

Carlos A. Fisher
Reg. No. 36,510
ALLERGAN SALES, INC.

Please direct all correspondence to:

Carlos A. Fisher (T2-7H)
Attorney of Record
ALLERGAN, INC.
2525 Dupont Drive
Irvine, CA 92612
Telephone: 714/246-4920
Fax: 714/246-4249

OIPE JC54
MAR 17 2003
PATENT & TRADEMARK OFFICE

1626/14

RECEIVED
APR 24 2003
TECH CENTER 1600/2900

DOCKET NO.: 17361(AP)
PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of Olejnik, et al.

Serial No: 09/904,018
Conf. No.: 1779
Filed: July 10, 2001

Group Art Unit: 1626

Examiner: Bennett, R.

For: COMPOSITIONS CONTAINING ALPHA-2-ADRNERGIC AGONIST COMPONENTS

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 (7 pgs.)
4) Terminal Disclaimer
5) Declaration of Orest Olejnik, Ph.D.

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

3/12/2003 (Date of Deposit)

BONNIE FERGUSON Name of person mailing correspondence

3/12/2003 Date of Signature

Bonnie Ferguson Signature

The fee has been calculated as shown below:

CLAIMS AS FILED

	CLAIMS REMAINING AFTER AMENDMENT	HIGHEST NO. PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE	
Total Claims	33	46	= 0 ×	$18	= $0.00
Independent Claims	6	3	= 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					$0.00

( ) 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: 3/11/03

Signature:

Carlos A. Fisher
Registration No. 36,510
Legal Department, T2-7H
ALLERGAN, INC.
2525 Dupont Drive
Irvine, CA 92612
Telephone: (714) 246-4920
Fax: (714) 246-4249

EXHIBIT D , TAB 11

OIPE JC54 MAR 17 2003 PATENT & TRADEMARK OFFICE

DOCKET NO. 17361 (AP)
PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of Olejnik, et al.

Serial No: 09/904,018

Filed: July 10, 2001

For: COMPOSITIONS CONTAINING ALPHA-2-ADRNERGIC AGONIST COMPONENTS

Group Art Unit: 1626

Examiner: Bennett, R.

RECEIVED
MAR 24 2003
TECH CENTER 1600/2900

DECLARATION OF OREST OLEJNIK, Ph.D.

Dear Sir,

I, Orest Olejnik, Ph.D., hereby declare as follows:

1. I received a B.Sc. degree in Pharmacy, with honors, from the Sunderland School of Pharmacy, England in 1977. In 1981 I was awarded a Ph.D. in Pharmaceutics by the University of Nottingham, Nottingham, England.

2. I have worked in the pharmaceutical development field as a pharmacist and in various managerial capacities since 1977. From 1991-1999 I was Director of Pharmaceutical Development at Allergan, Inc., in Irvine, California. I presently hold the position of Vice President of Pharmaceutical Sciences at Allergan.

3. I am a co-inventor of the present patent application 09/904,018, entitled "Compositions Containing Alpha-2-Adrenergic Agonist Components". I understand that the formerly pending claims were rejected under 35 USC 103 as obvious over US Patent 5,215,991 (the "Burke" patent) in view of Remington's Pharmaceutical Sciences, cited in the Form PTO-892 as part of Paper No. 7. I have reviewed each of these references.

4. The Burke patent references the presently claimed alpha-2-agonist 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline ("brimonidine"). The Burke patent discloses a multitude of different ingredients that may be contained in formulations containing brimonidine; among these are mentioned optional "vehicles" which may include, without limitation, polyvinyl alcohol, povidone (polyvinylpyrrolidone), hydroxypropylcellulose, poloxamers, carboxymethylcellulose (CMC), and

hydroxyethylcellulose. See Burke, column 5, line 28-34. Burke is silent concerning the purpose of these prospective vehicles.

5. Remington discloses that these listed polymers, including CMC, may be used as viscosity-increasing agents.

6. Neither Burke nor Remington discloses that CMC would have any characteristics that would motivate a person of ordinary skill in the art to choose it over other polymers in formulating a brimonidine solution.

7. Unlike the other listed polymers (polyvinyl alcohol, povidone (polyvinylpyrrolidone), hydroxypropylcellulose, poloxamers, and hydroxyethylcellulose), CMC is anionic at pH 7 or greater. The other listed polymers are non-ionic polymers. I have discovered as a result of work done and/or directed by me at Allergan that CMC possesses the surprising advantages of both increasing the solubility of brimonidine in solution, as shown in Table 1, and causing such solutions to have superior adherence to cell surfaces, including ocular surfaces such as the cornea. Polyvinyl alcohol was found not to possess both of these properties. Increased adherence of the CMC solution is particularly surprising given the fact that the corneal surface is negatively charged; one would expect less adherence in such a solution due to electrostatic repulsion, rather than increased adherence. This surprising result may be due to repulsive forces between the polymer and the cornea orienting the hydrophilic portions of the molecule away from the cornea, thus permitting the hydrophobic domains of these polymers to form an interaction with the lipid portion of the cell surface. With such increased adherence, the active ingredient in solution is placed in contact with the cell surface longer than would otherwise be the case.

8. It is also my belief that brimonidine solutions made using the other "vehicles" mentioned in the Burke patent would not possess this surprising combination of advantages. Therefore, the disclosures of Burke and Remington's in no way would render the presently claimed compositions obvious to the worker of ordinary (or even extraordinary) skill in the art.

9. 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,

Orest Olejnik, Ph.D.

EXHIBIT D , TAB 12

OIPE JC54
MAR 17 2003
PATENT & TRADEMARK OFFICE

DOCKET NO. 17361(AP)
PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of Olejnik et al

Serial No: 09/904,018

Filed: July 10, 2001

For: COMPOSITIONS CONTAINING ALPHA-2-AGONIST ADRENERGIC AGONIST COMPONENTS

Group Art Unit: 1615

Examiner: Bennett, R.

RECEIVED
MAR 24 2003
TECH CENTER 1600/2900

Commissioner of Patents
Washington, D.C. 20231

TERMINAL DISCLAIMER TO OBVIATE A PROVISIONAL DOUBLE PATENTING REJECTION OVER A PENDING PATENT APPLICATION

Dear Sir:

The owner, Allergan Sales, Inc., of 100 percent interest in the instant application hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application, which would extend beyond the expiration date of the full statutory term defined in 35 USC 154 and 156 and 173, as may be presently shortened by any terminal disclaimer, of any patent issuing on co-pending United States Patent Application No. 10/236,566. The owner hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and any patent issuing from the above- identified patent application are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors or assigns.

In making the above disclaimer, the owner does not disclaim the terminal part of any patent granted on the instant application that would extend to the expiration date of the full statutory term as defined in 35 USC 154 to 156 and 173 of any patent issuing from United States Patent Application No. 10/236,566, as presently shortened by any terminal disclaimer, in the event that it later: expires for failure to pay a maintenance fee, is held unenforceable, is found invalid by a court of competent jurisdiction, is statutorily disclaimed in whole or terminal

03/21/2003 HVUONG1 00000005 010885 09904018
01 FC:1614 110.00 CH

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

The undersigned is an attorney of record.

Date: 3/11/05

By: _____
Carlos A. Fisher
Reg. No. 36,510

ALLERGAN SALES, INC.

X Please charge the terminal disclaimer fee under 37 CFR 1.20(d) to Account No. 01-0885. A duplicate of this terminal disclaimer is enclosed.

Please direct all future correspondence to:

Carlos A. Fisher (T2-7H)
Attorney of Record
ALLERGAN, INC.
2525 Dupont Drive
Irvine, CA 92612
Telephone: 714/246-4920
Fax: 714/246-4249

EXHIBIT D , TAB 13

Interview Summary	Application No. 09/904,018	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: *10 April 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: *Claims 31-46*.

Identification of prior art discussed: _____.

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

Substance of Interview including description of the general nature of what was agreed to if an agreement was reached, or any other comments: *The attorney of record authorized the examiner to cancel claims 31-46.*.

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

THE FORMAL WRITTEN REPLY TO THE LAST OFFICE ACTION MUST INCLUDE THE SUBSTANCE OF THE INTERVIEW. (See MPEP Section 713.04). If a reply to the last Office action has already been filed, APPLICANT IS GIVEN 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.