EXHIBIT 1

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

ALLERGAN, INC., ALLERGAN SALES, LLC,
Plaintiffs,

VS.

ALCON, INC., ALCON LABORATORIES, INC. and ALCON RESEARCH, LTD.,
Defendants.

CIVIL ACTION NUMBER
04-968-GMS

COPY

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- CONFIDENTIAL - PURSUANT TO PROTECTIVE ORDER -

ORAL AND VIDEOTAPED DEPOSITION OF
RAMON L. ESPINO
April 18, 2005
Volume 1

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ORAL AND VIDEOTAPED DEPOSITION OF RAMON L. ESPINO, produced as a witness at the instance of the Plaintiffs, Allergan, Inc. and Allergan Sales, LLC, and duly sworn, was taken in the above-styled and -numbered cause on the 18th day of April, 2005, from 9:24 a.m. to 5:59 p.m., before Tommi Rutledge-Gray, CSR, RPR, and CRR in and for the State of Texas, reported by machine shorthand, at the Law Offices of Kelly, Hart & Hallman, P.C., 201 Main Street, Suite 2500, Fort Worth, Texas 76102, in accordance with Notice of Deposition, and pursuant to the Federal Rules of Civil Procedure.

APPEARANCES

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at pH 7.5, what was the percentage Brimonidine in solution?

A. That was 100.18.

Q. So what does that mean about solution of 0.15% Brimonidine -- no. Strike that.

So over the pH range 6.0 to 7.5, did you see any evidence that Povidone acted to enhance solubility of Brimonidine in this study that you did in 2003?

A. No. I don't see any evidence.

Q. Okay. And looking at Exhibit 17, is the -- does the table on the second page of Exhibit 17 represent the results of the solubility study that you performed in 2004?

A. Yes.

Q. And over the pH range that you studied there, pH 6.6 to pH 7.5, did you see any evidence that Providone acted to enhance the solubility of Brimonidine Tartrate?

A. No, I don't.

Q. Okay. Did you do any studies on the sol -- the solubility of Brimonidine that you have not testified about here today?

A. No.

Q. To your knowledge, did anyone else at Alcon

perform any solubility testing on Brimonidine?
A. No.
Q. Who did the HPLC measurements in each of the two studies that you did in 2003 and 2004?
A. It was DiMarcos Pereira and I, and Pat Underwood and I.
Q. Okay. And who did the calculations in those studies to obtain the results?
A. I -- I did them, and they -- they did them also.
Q. Okay. Did you study any viscosity modifiers other than Povidone or HEC when you were formulating Brimonidine PQ?
A. No, I did not.
Q. Take a look at Exhibit 12 for a moment.
A. (Witness complies.)
Q. And is Exhibit 12 the '210 patent?
A. That is correct.
Q. Can you turn to Table IV.
A. Table IV, yes.
Q. Do you know how the data in Table IV was derived?
A. I think it was derived from HPLC measurements of Table III.
Q. Okay. Did you reach any conclusions about the

data in Table IV?
A. No, I did not.
Q. Okay. You testified earlier that you didn't understand what you read off the '210 patent. Why was that?
A. Because I cannot see making more of Brimonidine Tartrate from -- from less at pH 6.8 without CMC.
Q. So is that why you didn't understand the -- the '210 patent?
A. That's right.
MS. MULLALLY: Okay. I don't have any further questions.

FURTHER EXAMINATION

BY MR. SHEAR:
Q. Just a few follow-ups. Mr. Espino, you were just asked about Exhibit 17, which is the results of the second study that you performed.
Do you have Exhibit 17 in front of you?
A. Exhibit 17, (indicating)?
Q. 17. Exhibit 17 was sent for statistical analysis, was it not? The results of Exhibit

EXHIBIT 2

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

ALLERGAN, INC., ALLERGAN SALES, LLC, Plaintiffs, v. ALCON, INC., ALCON LABORATORIES, INC., and ALCON RESEARCH, LTD., Defendants.	Civil Action No. 04-968-GMS

JOINT CLAIM CHART

'337 Patent

Asserted Claim	**Agreed Upon Construction**	**Allergan's Proposed Construction**	**Alcon's Proposed Construction**
Claim 1			
1. A therapeutically effective ophthalmic composition comprising:	The claim requires a therapeutically effective ophthalmic composition, and the term "therapeutically effective" is used in its ordinary sense.	The parties do not dispute the construction of this limitation.	The parties do not dispute the construction of this limitation.
an alpha-2-adrenergic agonist component in an amount effective to provide a therapeutic benefit to a patient in whom the composition is administered; and	The claimed composition must contain an alpha-2-adrenergic agonist component in an amount that is effective to provide a therapeutic benefit to a patient.	The parties do not dispute the construction of this limitation.	The parties do not dispute the construction of this limitation.
a solubility enhancing component other than a cyclodextrin	The parties dispute the construction of this limitation.	The claimed composition contains a solubility	The claimed composition must contain an anionic component, other than a cyclodextrin, in an

Asserted Claim	Agreed Upon Construction	Allergan's Proposed Construction	Alcon's Proposed Construction
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.		enhancing component, which is a component that enhances the solubility of the alpha-2-adrenergic agonist component, and any solubility enhancing component other than a cylclodextrin is covered by the claim. The solubility enhancing component must be present in such an amount that the solubility of the alpha-2-adrenergic agonist component in the composition is increased relative to its solubility in a similar composition without the solubility enhancing component. Support for proposed construction: '337 patent, abstract, col. 2, lines 13-20, col. 4, lines 60-65, col. 6, lines 17-41, '337 patent file history, Reply to Office Action, Dated June 16, 2003.	amount effective to increase the solubility of the alpha-2-adrenergic agonist component in the composition relative to the solubility of the alpha-2-adrenergic agonist component in an otherwise identical composition without the anionic component. In addition, the "solubility enhancing component" cannot be polyvinyl alcohol, povidone (polyvinylpyrrolidone), hydroxypropylcellulose, poloxamers or hydroxymethylcellulose. Support for proposed construction: Application No. 09/904,018 (parent application of the application which issued as the '337 patent): Office Action mailed September 18, 2002; Response to Restriction Requirement received by PTO on October 22, 2002; Office Action dated January 9, 2003; Interview Summary, mailed 3/3/03; Reply to Office Action, received by the PTO March 17, 2003 including Declaration of Orest Olejnik; '337 patent, Office Action, mailed March 13, 2003; Reply to Office Action, dated June 16, 2003.

Asserted Claim	Agreed Upon Construction	Allergan's Proposed Construction	Alcon's Proposed Construction
Claim 2			
2. The composition of claim 1 wherein the alpha-2-adrenegic component is selected from the group consisting of imino-imidazolines, imidazolines, imidazoles, azepines, thiazines, oxazolines, guanidines, catecholamines, derivatives thereof, and mixtures thereof.	Claim 2 contains all the limitations of claim 1, with the additional requirement that the alpha-2-adrenergic agonist component must be: an imino-imidazoline, imidazoline, imidazole, azepine, thiazine, oxazoline, guanidine, catecholamine, derivative of one of the foregoing, or a mixture of one of the foregoing.	The parties do not dispute the construction of this limitation.	The parties do not dispute the construction of this limitation.
Claim 3			
3. The composition of claim 1 wherein the therapeutically active component includes a quinoxaline component.	Claim 3 includes all the limitations of claim 1, with the further requirement that the composition must contain a quinoxaline component.	The parties do not dispute the construction of this limitation.	The parties do not dispute the construction of this limitation.
Claim 4			
4. The composition of claim 3 wherein the quinoxaline component is selected from the group consisting of quinoxaline, derivatives thereof, and mixtures thereof.	Claim 4 includes all the limitations of claims 1 and 3, with the further requirement that the quinoxaline component must be a quinoxaline, a derivative of quinoxaline, or mixture of two or more of the foregoing.	The parties do not dispute the construction of this limitation.	The parties do not dispute the construction of this limitation.

Asserted Claim	Agreed Upon Construction	Allergan's Proposed Construction	Alcon's Proposed Construction
Claim 6			
6. 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 component relative to the solubility in a biological environment of an identical alpha-2-adrenergic agonist component in a similar composition without the solubility enhancing component.	The parties dispute the construction of this limitation.	Claim 6 includes all the limitations of claim 1, with the further requirement that the solubility enhancing component is effective to increase the solubility in a biological environment of the alpha-2-adrenergic agonist component relative to its solubility in a similar composition without the solubility enhancing component. Support for proposed construction: '337 patent, col. 1, lines 58-64, col. 4, lines 41-47.	Claim 6 contains all the limitations of claim 1, with the further requirement that the "solubility enhancing component" must be effective to increase the solubility in a biological environment of the alpha-2-adrenergic agonist component relative to the solubility in the same biological environment of the alpha-2-adrenergic agonist component in an otherwise identical composition without the "solubility enhancing component." Support for proposed construction: As relevant to the construction of claim 6, Alcon incorporates its comment to claim 1.
Claim 9			
The composition of claim 1 which further comprises an effective amount of a preservative.	Claim 9 includes all the limitations of claim 1 with the further requirement that the composition must contain a component that assists in the preservation of the composition.	The parties do not dispute the construction of this limitation.	The parties do not dispute the construction of this limitation.

Asserted Claim	Agreed Upon Construction	Allergan's Proposed Construction	Alcon's Proposed Construction
Claim 10			
The composition of claim 6 which further comprises an effective amount of a preservative.	Claim 10 includes all the limitations of claim 6 with the further requirement that the composition must contain an effective amount of a component that assists in the preservation of the composition.	The parties do not dispute the construction of this limitation.	The parties do not dispute the construction of this limitation.

'834 Patent

Asserted Claim	Agreed Upon Construction	Allergan's Proposed Construction	Alcon's Proposed Construction
Claim 1			
1. A therapeutically effective aqueous ophthalmic composition comprising:	The claim requires a therapeutically effective ophthalmic composition, and the term "therapeutically effective" is used in its ordinary sense.	The parties do not dispute the construction of this limitation.	The parties do not dispute the construction of this limitation.
up to about 0.15% (w/v) of 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline tartrate,	The parties dispute the construction of this limitation.	The claimed composition contains up to approximately 0.15% (w/v) brimondine tartrate. Support for proposed construction: The term "about" is used in its ordinary sense, meaning "approximately." *See Merck & Co. v. Teva Pharms., Inc.*, 395 F.3d 1364 (Fed. Cir. 2005). *See also* '834 patent, Figure 1, col. 1, lines 33-53, col. 2, lines 48-52, col. 3, lines 23-36, col. 6, lines 8-16, col. 11, lines 1-6,	The claimed composition must contain up to 0.155% (w/v) (the upper limit of 0.15 ± 0.005% (w/v)) of brimondine tartrate. The specification (including the claims as originally filed) and prosecution history of the '834 patent only reflect testing of brimonidine tartrate solutions at concentrations of 0.5% (w/v) and 0.2% (w/v) and thus provide no teaching or

Asserted Claim	Agreed Upon Construction	Allergan's Proposed Construction	Alcon's Proposed Construction
		Example 2 and descriptive text, Table IV and descriptive text, Application No. 09/904,018 (parent application of the application which issued as the '834 patent, including the original claims), '834 patent file history, Reply to Office Action, dated Mar. 24, 2003.	guidance supporting the terms "up to about 0.15% (w/v)," "up to 0.15% (w/v)," or "about 0.15% (w/v)" nor do they disclose that such compositions are within the scope of the alleged invention. In *Merck & Co. v. Teva Pharms., Inc.*, 395 F.3d 1364 (Fed. Cir. 2005), the court rejected the patentee's attempt to define the terms "about 70 mg" and "about 35 mg" as limited to the precise numerical values disclosed, without any surrounding range. Thus, in order to supply a range, but in light of the absence of any teaching in the specification as guidance for the same, Alcon proposes that the term "about" be interpreted to encompass the full range of values that would normally be rounded up or down to 0.15%.
the composition having a pH of about 7.0 or greater,	The parties dispute the construction of this limitation.	The claimed composition has a pH of approximately 7.0 or greater. Support for proposed construction: The term "about" is used	The composition must have a pH of 6.95 (the lower limit of 7.0 $\pm$ 0.05) or greater. The specification (including the

Asserted Claim	Agreed Upon Construction	Allergan's Proposed Construction	Alcon's Proposed Construction
		in its ordinary sense, meaning "approximately." *See Merck & Co. v. Teva Pharms., Inc.*, 395 F.3d 1364 (Fed. Cir. 2005). *See also* '834 patent, Figure 1, col. 4, lines 22-33, col. 11, lines 1-6, Example 2 and descriptive text, Application No. 09/904,018 (parent application of the application which issued as the '834 patent, including the original claims), '834 patent file history, Reply to Office Action, dated Mar. 24, 2003.	claims as originally filed) and the prosecution history of the '834 patent provide no teaching regarding the scope of the pH limitation. Thus, Alcon proposes that the term "about" be interpreted to encompass the full range of values that would normally be rounded up or down to pH 7.0.
and the 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline tartrate being soluble in the composition at about 21° C.	The parties dispute the construction of this limitation.	The brimonidine tartrate must be soluble in the composition at approximately 21° C. Support for proposed construction: The term "about" is used in its ordinary sense, meaning "approximately." *See Merck & Co. v. Teva Pharms., Inc.*, 395 F.3d 1364 (Fed. Cir. 2005). *See also* '834 patent, Figure 1, Example 2 and descriptive text, Application No. 09/904,018 (parent application of the application which issued as the '834 patent, including the original claims), '834	The brimondine tartrate must be soluble in the composition at 21 ± 0.5C The specification (including the claims as originally filed) and the prosecution history of the '834 patent provide no teaching regarding the scope of the temperature limitation. Thus, Alcon proposes that the term "about" be interpreted to encompass the full range of values that would normally be rounded up or down to a temperature of 21°C.

Asserted Claim	Agreed Upon Construction	Allergan's Proposed Construction	Alcon's Proposed Construction
		patent file history, Reply to Office Action, dated Mar. 24, 2003.	
Claim 2			
2. The composition of claim 1 which includes up to 0.15% (w/v) of 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline tartrate.	Claim 2 includes all the limitations of claim 1, with the additional requirement that the composition must include up to 0.15% (w/v) brimonidine tartrate.	The parties do not dispute the construction of this limitation.	The parties do not dispute the construction of this limitation.
Claim 3			
3. The composition of claim 1 which includes about 0.15% (w/v) of 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline tartrate.	The parties dispute the construction of this limitation.	Claim 3 includes all the limitations of claim 1, with the additional requirement that the composition must include approximately 0.15% brimonidine tartrate. Support for proposed construction: The term "about" is used in its ordinary sense, meaning "approximately." *See Merck & Co. v. Teva Pharms., Inc.*, 395 F.3d 1364 (Fed. Cir. 2005). *See also* '834 patent, Figure 1, col. 1, lines 33-53, col. 2, lines 48-52, col. 3, lines 23-36, col. 6, lines 8-16, col. 11, lines 1-6, Example 2 and descriptive text, Table IV and descriptive text, Application No. 09/904,018 (parent application of the application which	Claim 3 contains all the limitations of claim 1, with the additional requirement that the composition must include 0.15% ± 0.005% (w/v) brimondine tartrate. Support for proposed construction: As relevant to the construction of claim 3, Alcon incorporates its comments to claim 1.

Asserted Claim	Agreed Upon Construction	Allergan's Proposed Construction	Alcon's Proposed Construction
		issued as the '834 patent, including the original claims), '834 patent file history, Reply to Office Action, dated Mar. 24, 2003.	
Claim 4			
4. The composition of claim 1 which included 0.15% (w/v) of 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline tartrate.	Claim 4 includes all the limitations of claim 1, with the additional requirement that the composition must include 0.15% (w/v) brimonidine tartrate.	The parties do not dispute the construction of this limitation.	The parties do not dispute the construction of this limitation.
Claim 5			
5. The composition of claim 1 having a pH of 7.0 or greater.	Claim 5 includes all the limitations of claim 1, with the additional requirement that the pH of the composition must be 7.0 or greater.	The parties do not dispute the construction of this limitation.	The parties do not dispute the construction of this limitation.
Claim 6			
6. 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.	Claim 6 includes all the limitations of claim 1 and further requires that the composition must contain either an oxy-chloro or quaternary ammonium preservative in an amount effective to assist in preserving the composition.	The parties do not dispute the construction of this limitation.	The parties do not dispute the construction of this limitation.
Claim 8			
8. The composition of claim 1 which is substantially free of anionic cellulosic derivatives.	Claim 8 includes all the limitations of claim 1 and further requires that the composition is	The parties do not dispute the construction of this limitation.	The parties do not dispute the construction of this limitation.

Asserted Claim	Agreed Upon Construction	Allergan's Proposed Construction	Alcon's Proposed Construction
	substantially free of anionic cellulosic derivatives.		
Claim 9			
The composition of claim 1 which is substantially free of carboxymethyl cellulose.	Claim 9 includes all the limitations of claim 1 and further requires that the composition is substantially free of carboxymethyl cellulose.	The parties do not dispute the construction of this limitation.	The parties do not dispute the construction of this limitation.
Claim 10			
10. A therapeutically effective aqueous ophthalmic composition comprising:	The claim requires a therapeutically effective ophthalmic composition, and the term "therapeutically effective" is used in its ordinary sense.	The parties do not dispute the construction of this limitation.	The parties do not dispute the construction of this limitation.
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 parties dispute the construction of this limitation.	The claimed composition contains up to approximately 0.15% (w/v) brimondine, salts of brimonidine, esters of brimonidine, or mixtures of the foregoing. Support for proposed construction: The term "about" is used in its ordinary sense, meaning "approximately." *See Merck & Co. v. Teva Pharms., Inc.*, 395 F.3d 1364 (Fed. Cir. 2005). See also '834 patent, Figure 1, col. 1, lines 33-53, col. 2, lines 48-52, col. 3, lines 23-36, col. 6, lines 8-16, col. 11, lines 1-6, Example 2 and	The claimed composition must contain up to 0.155% (w/v) (the upper limit of 0.15 ± 0.005% (w/v)) of brimondine, salts of brimonidine, esters of brimonidine, or mixtures of two or more of the foregoing. The specification (including the claims as originally filed) and prosecution history of the '834 patent only reflect testing of brimonidine tartrate solutions at concentrations of 0.5% (w/v) and 0.2% (w/v) and thus provide no teaching or

Asserted Claim	Agreed Upon Construction	Allergan's Proposed Construction	Alcon's Proposed Construction
		descriptive text, Table IV and descriptive text, Application No. 09/904,018 (parent application of the application which issued as the '834 patent, including the original claims), '834 patent file history, Reply to Office Action, dated Mar. 24, 2003.	guidance supporting the terms "up to about 0.15% (w/v)," "up to 0.15% (w/v)," or "about 0.15% (w/v)" nor do they disclose that such compositions are within the scope of the alleged invention. In *Merck & Co. v. Teva Pharms., Inc.*, 395 F.3d 1364 (Fed. Cir. 2005), the court rejected the patentee's attempt to define the terms "about 70 mg" and "about 35 mg" as limited to the precise numerical values disclosed, without any surrounding range. Thus, in order to supply a range, but in light of the absence of any teaching in the specification as guidance for the same, Alcon proposes that the term "about" be interpreted to encompass the full range of values that would normally be rounded up or down to 0.15%.
the composition having a pH of about 7.0 or greater,	The parties dispute the construction of this limitation.	The claimed composition has a pH of approximately 7.0 or greater. Support for proposed construction: The term "about" is used	The claimed composition must have a pH of 6.95 (the lower limit of 7.0 ± 0.05) or greater. The specification (including the

Asserted Claim	Agreed Upon Construction	Allergan's Proposed Construction	Alcon's Proposed Construction
		in its ordinary sense, meaning "approximately." *See Merck & Co. v. Teva Pharms., Inc.*, 395 F.3d 1364 (Fed. Cir. 2005). *See also* '834 patent, Figure 1, col. 4, lines 22-33, col. 11, lines 1-6, Example 2 and descriptive text, Application No. 09/904,018 (parent application of the application which issued as the '834 patent, including the original claims), '834 patent file history, Reply to Office Action, dated Mar. 24, 2003.	claims as originally filed) and the prosecution history of the '834 patent provide no teaching regarding the scope of the pH limitation. Thus, Alcon proposes that the term "about" be interpreted to encompass the full range of values that would normally be rounded up or down to pH 7.0.
and the component being soluble in the composition at about 21° C.	The parties dispute the construction of this limitation.	The brimonidine tartrate must be soluble in the composition at approximately 21° C. Support for proposed construction: The term "about" is used in its ordinary sense, meaning "approximately." *See Merck & Co. v. Teva Pharms., Inc.*, 395 F.3d 1364 (Fed. Cir. 2005). *See also* '834 patent, Figure 1, Example 2 and descriptive text, Application No. 09/904,018 (parent application of the application which issued as the '834 patent, including the original claims), '834 patent file history,	The component must be soluble in the composition at 21 ± .5°C. The specification (including the claims as originally filed) and the prosecution history of the '834 patent provide no teaching regarding the scope of the temperature limitation. Thus, Alcon proposes that the term "about" be interpreted to encompass the full range of values that would normally be rounded up or down to a temperature of 21°C.

Asserted Claim	Agreed Upon Construction	Allergan's Proposed Construction	Alcon's Proposed Construction
		Reply to Office Action, dated Mar. 24, 2003.	
Claim 11			
11. The composition of claim 10 which includes up to 0.15% (w/v) of the component.	Claim 11 includes all the limitations of claim 10, with the additional requirement that the composition must include up to 0.15% (w/v) of the component selected from the group described in claim 10.	The parties do not dispute the construction of this limitation.	The parties do not dispute the construction of this limitation.
Claim 12			
12. The composition of claim 10 which includes about 0.15% (w/v) of the component	The parties dispute the construction of this limitation.	Claim 12 includes all the limitations of claim 10, with the additional requirement that the composition must include approximately 0.15% (w/v) of the component selected from the group described in claim 10. Support for proposed construction: The term "about" is used in its ordinary sense, meaning "approximately." *See Merck & Co. v. Teva Pharms., Inc.*, 395 F.3d 1364 (Fed. Cir. 2005). *See also* '834 patent, Figure 1, col. 1, lines 33-53, col. 2, lines 48-52, col. 3, lines 23-36, col. 6, lines 8-16, col. 11, lines 1-6, Example 2 and descriptive text,	The claimed composition must include all the limitations of claim 10, with the additional requirement that the composition must include 0.15 ± 0.005% (w/v) of the component listed in claim 10. As relevant to the construction of claim 12, Alcon incorporates its comments to claim 10.

Asserted Claim	Agreed Upon Construction	Allergan's Proposed Construction	Alcon's Proposed Construction
		Table IV and descriptive text, Application No. 09/904,018 (parent application of the application which issued as the '834 patent, including the original claims), '834 patent file history, Reply to Office Action, dated Mar. 24, 2003.	
Claim 13			
13. The composition of claim 10 which includes 0.15% (w/v) of the component	Claim 13 includes all the limitations of claim 10, with the additional requirement that the composition must include 0.15% (w/v) of the component selected from the group described in claim 10.	The parties do not dispute the construction of this limitation.	The parties do not dispute the construction of this limitation.
Claim 14			
14. The composition of claim 10 having a pH of 7.0 or greater.	Claim 14 includes all the limitations of claim 10, with the additional requirement that the pH of the composition must be 7.0 or greater.	The parties do not dispute the construction of this limitation.	The parties do not dispute the construction of this limitation.
Claim 17			
17. The composition of claim 10 which is substantially free of anionic cellulosic derivatives.	Claim17 includes all the limitations of claim 10 and further requires that the composition is substantially free of anionic cellulosic derivatives.	The parties do not dispute the construction of this limitation.	The parties do not dispute the construction of this limitation.
Claim 18			
18. The composition of claim 10 which is	Claim 18 includes all the limitations of claim 10 and further	The parties do not dispute the construction of this	The parties do not dispute the construction of this

Asserted Claim	Agreed Upon Construction	Allergan's Proposed Construction	Alcon's Proposed Construction
substantially free of carboxymethyl cellulose.	requires that the composition is substantially free of carboxymethyl cellulose.	limitation.	limitation.
Claim 20			
20. The composition of claim 10 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.	Claim 20 includes all the limitations of claim 10 and further requires that the composition must contain either an oxy-chloro or quaternary ammonium preservative in an amount effective to assist in preserving the composition.	The parties do not dispute the construction of this limitation.	The parties do not dispute the construction of this limitation.

FISH & RICHARDSON P.C.

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EXHIBIT 3

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MAR 2 4 2003
PATENT & TRADEMARK OFFICE

#63
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MAR 28 2003
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DOCKET NO: 7361CON(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 CV0111 00000051 010885 10236566
01 FC:1202 72.00 CH

AMENDMENTS TO THE CLAIMS

Kindly make the following amendments to the claims:

R1

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

R2

6 53. (Amended) The composition of claim 1 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

R3

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

R4

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

20 68. (New) The composition of claim 10 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,

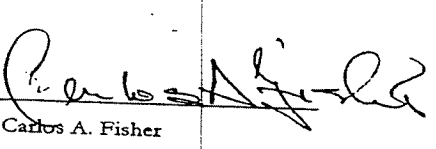
lowering the concentration, when the pH is above about 7.0 unexpectedly had no significant effect on therapeutic efficacy, when compared to the 0.2% formulation.

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

Group Art Unit: 1626

Examiner: Bennett, R.

For: COMPOSITIONS CONTAINING ALPHA-2-ADRENERGIC 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 (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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