Part 4
to
EXHIBIT G

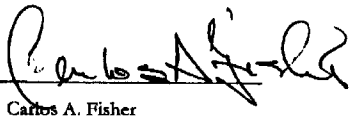
lowering the concentration, when the pH is above about 7.0 unexpectedly had no significant effect on therapeutic efficacy, when compared to the 0.2% formulation.

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: 

Carlos A. Fisher
Reg. No. 36,510
ALLERGAN, 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 JC48 MAR 24 2003 PATENT & TRADEMARK OFFICE

1626
RECEIVED
MAR 28 2003
TECH CENTER 1600/2900

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

OIPE JC48 MAR 24 2003 PATENT & TRADEMARK OFFICE

RECEIVED MAR 28 2003 TECH CENTER 1600/2900

DOCKET NO. 17361CON/APP
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: 1626

Examiner: Bennett, R.

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

Received May 9, 2001; accepted August 7, 2001.

Members of the Brimonidine-Purite Study Groups 1 and 2 are listed in the Appendix at the end of this article.

Supported by Allergan (Irvine, CA).

Address correspondence and reprint requests to L. Jay Katz, MD, Wills Eye Hospital, 900 and Walnut Street, Philadelphia, PA 19107-5599. E-mail: ljk22222@aol.com

THIS MATERIAL MAY BE PROTECTED BY COPYRIGHT LAW (17 USC)

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 ≥ 22 mm Hg, ≤ 34 mm Hg in each eye after washout, with between-eye IOP asymmetry ≤ 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.

This page intentionally left blank

AGN221652

Efficacy Variables

The primary efficacy variable was IOP. Diurnal IOP was measured at approximately 8 AM (before the morning drop), 10 AM, 3 PM (before the afternoon drop), and 5 PM at baseline, week 6, and at months 3, 6, and 12. The IOP was also measured at approximately 8 AM (before the morning drop) and 10 AM at week 2 and month 9.

Other efficacy variables included clinical success as evaluated by the investigator (regardless of whether a physician recommended continuation of study medication for the patient), subject satisfaction evaluation, and subject comfort evaluation using standardized scales.

Other measures that were evaluated included adverse events, visual acuity, cup/disc ratio, biomicroscopy, ophthalmoscopy, visual fields, heart rate, and systolic and diastolic blood pressure. The severity of adverse events was assessed based on the following guidelines: mild (awareness of sign or symptom, but easily tolerated), moderate (discomfort enough to cause interference with usual activity) and severe (incapacitating or unable to work or perform usual activities).

Statistical Analysis

The primary variables of analysis for efficacy were mean IOP and the mean change in IOP from baseline. These IOP data were analyzed using both the intent-to-treat with last observation carried forward and per-protocol populations. The per-protocol population consisted of observed cases. Only patients who met the protocol entry criteria, had no major protocol violations, received study medication, and had at least one follow-up visit were included in the per-protocol analysis, and only data from visits within specified time windows were included. Decisions for per-protocol exclusions were made before unmasking of the treatment groups for analysis. Safety data were analyzed using the intent-to-treat population. For comparison of treatment efficacy, both noninferiority and a two-sided paired t test for superiority were performed. Noninferiority criteria were set by the US Food and Drug Administration. Criteria were tested by constructing a two-sided 95% confidence interval for the between-group difference between experimental drug and brimonidine in mean IOP. If the upper limit of 95% confidence interval at all time points did not exceed 1.5 mm Hg, brimonidine-Purite was considered at least as effective as brimonidine.

Nominal categorical data such as sex and race were analyzed by the Cochran-Mantel-Haenszel method and continuous variables such as age and blood pressure were analyzed using a two-way analysis of variance with factors of treatment group and investigator site. Adverse events were analyzed using the Pearson χ^2 test or Fisher exact test. Ordinal categorical variables such as comfort and safety data were analyzed using the stratum (investigator site) adjusted Kruskal-Wallis and Wilcoxon rank-sum test.

RESULTS

Subject Demographics

The demographics and clinical characteristics of patients taking brimonidine-Purite 0.15% three times daily, brimonidine-Purite 0.2% three times daily, and brimonidine 0.2% three times daily are summarized in Table 1. No significant between-group differences were noted in baseline demographics, which included mean patient age, gender, race, and iris color.

Efficacy

Criteria for the per-protocol analysis were met by 97.9% (1,123 of 1,147) of patients (brimonidine-Purite 0.15%, 97.6% [372 of 381 patients]; brimonidine-Purite 0.2%, 97.9% [375 of 383 patients]; brimonidine 0.2%, 98.2% [376 of 383 patients]) and 92% of all data points were included with a similar distribution across the treatments. Twenty-four patients did not meet the entry criteria as defined in the study protocol and were excluded from the efficacy analysis. Other key reasons for patient data exclusions from the per-protocol analysis included use of excluded medications during the study, inappropriate instillation of study medications, and visits occurring outside of visit windows. There was no significant difference in the IOP results between the intent-to-treat and per-protocol analyses, and the per-protocol results are presented. The conclusions drawn from either intent-to-treat or per-protocol populations were the same.

Overall IOP Efficacy

At baseline, mean IOP was similar across the three treatment groups at each time point. Baseline mean IOP at 10 AM was 23.6 mm Hg (with an approximate SD of 3.2 mm Hg). Baseline mean IOP at 8 AM was 24.9 mm Hg (with an approximate SD of 2.7 mm Hg) (Fig. 1 and 2). Over the next 12 months, the difference in mean IOP at 10 AM (morning peak) (Fig. 1) and 8 AM (morning trough) (Fig. 2) between brimonidine-Purite 0.15% and brimonidine 0.2% was less than or equal to 0.4 mm Hg.

The mean IOP for each group was within 1 mm Hg of

TABLE 1. *Demographics and clinical characteristics of patients on brimonidine-Purite 0.15%, brimonidine-Purite 0.2%, and brimonidine 0.2%*

	Brimonidine-Purite 0.15% (n = 381)		Brimonidine-Purite 0.2% (n = 383)		Brimonidine 0.2% (n = 383)		Total (n = 1147)		
Variable	No.	(%)	No.	(%)	No.	(%)	No.	(%)	P
Age (years)									0.460
Mean	63.4		63.8		62.7		63.3		
SD	12.8		12.1		12.6		12.5		
Min	22.4		25.4		25.2		22.4		
Max	88.8		90.4		93.4		93.4		
Median	64.7		65.8		64.2		64.7		
Sex									0.845
Male	169	44.4%	162	42.3%	167	43.6%	498	43.4%	
Female	212	55.6%	221	57.7%	236	56.4%	649	56.6%	
Race									0.377
Caucasian	303	79.5%	298	77.8%	305	79.6%	906	79.0%	
Black	48	12.6%	59	15.4%	47	12.3%	154	13.4%	
Asian	2	0.5%	1	0.3%	3	0.8%	6	0.5%	
Hispanic	28	7.3%	23	6.0%	26	6.8%	77	6.7%	
Other	0	0.0%	2	0.5%	2	0.5%	4	0.3%	
Iris color									0.468
Blue	113	29.7%	108	28.2%	111	29.0%	332	28.9%	
Brown	179	47.0%	196	51.2%	183	47.8%	558	48.6%	
Green	23	6.0%	18	4.7%	18	4.7%	59	5.1%	
Hazel	59	15.5%	58	15.1%	68	17.8%	185	16.1%	
Other	7	1.8%	3	0.8%	3	0.8%	13	1.1%	

the mean IOP in the other groups at all visits and all time points, showing comparable IOP-lowering capabilities.

Brimonidine-Purite 0.15% Versus Brimonidine 0.2%

There were no statistically significant differences in diurnal mean IOP measurements between brimonidine-Purite 0.15% and brimonidine 0.2%, except at the 5-PM time point at month 3 (P = 0.046) where the mean IOP difference was 0.5 mm Hg in favor of brimonidine 0.2%. There were no statistically significant differences in the mean changes from baseline in diurnal IOP measurements, except for the 10-AM time point at week 2 (P = 0.015), the 5-PM time point at month 3 (P = 0.010), and the 5-PM time point at month 6 (P = 0.004). The mean

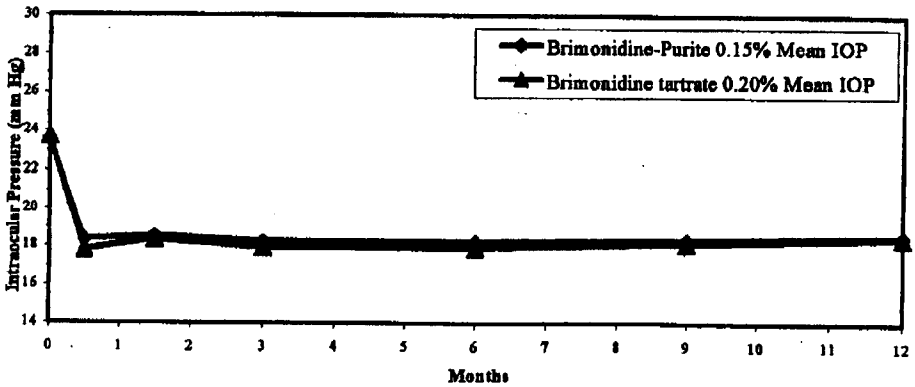


FIG. 1. Efficacy graph at 10 AM (peak) showing mean intraocular pressure of patients with glaucoma or ocular hypertension during 12-month treatment with brimonidine-Purite 0.15% and brimonidine 0.2% (Alphagan). The difference in mean intraocular pressure between the treatment groups was less than or equal to 0.4 mm Hg at all time points. All standard errors were less than 0.180.

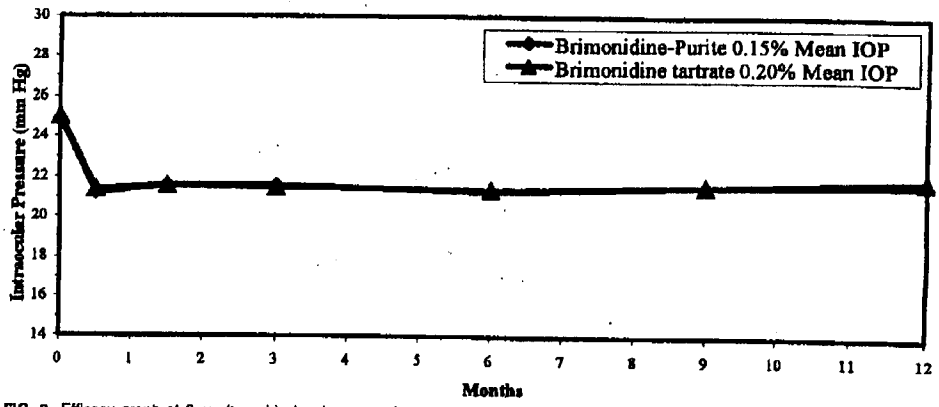


FIG. 2. Efficacy graph at 8 AM (trough) showing mean intraocular pressure of patients with glaucoma or ocular hypertension during 12-month treatment with brimonidine-Purite 0.15% and brimonidine 0.2% (Alphagan). All standard errors were less than 0.211.

change from baseline IOP difference was 0.6, 0.7, and 0.9 mm Hg, respectively favoring brimonidine 0.2%. The noninferiority criteria were satisfied because 40/40 of the upper limits of 95% confidence intervals were less than or equal to 1.5 mm Hg, with 36/40 less than or equal to 1.0 mm Hg (mean IOP and mean change from baseline IOP), showing that brimonidine-Purite 0.15% was comparable in efficacy with brimonidine 0.2%.

Brimonidine-Purite 0.15% Versus Brimonidine-Purite 0.2%

There were no statistically significant differences observed in mean IOP or mean changes from baseline in diurnal IOP measurements between brimonidine-Purite 0.15% and brimonidine-Purite 0.2%, except at the 5-PM time point at month 3 ($P = 0.027$, mean IOP), the 10-AM time point at month 9 ($P = 0.009$, mean IOP), and the 10-AM time point at month 12 ($P = 0.011$, mean IOP). The mean IOP difference was 0.6, 0.8, and 0.8 mm Hg, respectively, favoring brimonidine-Purite 0.2%. The noninferiority criteria were satisfied because 40/40 of the upper limits of 95% confidence intervals were less than or equal to 1.5 mm Hg, with 35/40 less than or equal to 1.0 mm Hg (mean IOP and mean changes from baseline IOP), showing that brimonidine-Purite 0.15% was comparable in efficacy with brimonidine-Purite 0.2%.

Brimonidine-Purite 0.2% Versus Brimonidine 0.2%

In the comparison of brimonidine-Purite 0.2% and brimonidine 0.2%, there were no statistically significant differences observed in mean IOP or mean changes from baseline in diurnal IOP measurements except for the 10-AM time point at month 9 ($P = 0.045$, mean IOP), the 10-AM time point at month 12 ($P = 0.018$, mean IOP), and the 5-PM time point at month 12 ($P = 0.041$, mean IOP). The average difference in mean IOP and mean changes from baseline in IOP difference was –0.6, –0.8, and –0.7 mm Hg, respectively, favoring brimonidine-Purite 0.2%. The only measurement favoring brimonidine 0.2% was at the 10-AM time point at month 6 (mean change from baseline IOP difference of 0.7 mm Hg, $P = 0.019$). The noninferiority criteria were satisfied because 40/40 of the upper limits of the 95% confidence intervals were less than or equal to 1.5 mm Hg, with 37/40 less than or equal to 1.0 mm Hg (mean IOP and mean changes from baseline IOP), showing that brimonidine-Purite 0.2% was comparable in efficacy with brimonidine 0.2%.

Safety

The following results were analyzed as intent-to-treat, and all data points were considered. Throughout the study, patients were monitored for signs and symptoms of adverse events (Table 2). Investigators rated the majority of adverse events as mild or moderate in severity. The overall frequency of treatment-related adverse events reported was fewer in the brimonidine-Purite 0.15% than with brimonidine-Purite 0.2% or brimonidine 0.2%. There was a lower incidence rate of allergic conjunctivitis, conjunctival hyperemia, and oral dryness favoring brimonidine-Purite 0.15% compared

TABLE 2. *Summary of treatment-related adverse events of patients with glaucoma or ocular hypertension during twelve-month treatment with brimonidine-Purite 0.15%, brimonidine-Purite 0.2%, and brimonidine 0.2% (among group P-values). The second P-value is a summary of possible, probable, and definite treatment-related adverse events in pairwise comparison of patients with glaucoma or ocular hypertension during twelve-month treatment with brimonidine-Purite 0.15 and brimonidine 0.2%*

Adverse event	Brimonidine-Purite 0.15% (n = 381) No. (%)	Brimonidine-Purite 0.2% (n = 383) No. (%)	Brimonidine 0.2% (n = 383) No. (%)	Amongst group P	Brimonidine-Purite 0.15 vs. brimonidine 0.2% P
Allergic conjunctivitis	35 (9.2%)	56 (14.6%)	60 (15.7%)	0.018	0.007
Oral dryness	20 (5.3%)	36 (9.4%)	40 (10.4%)	0.024	0.008
Conjunctival hyperemia	69 (18.2%)	81 (21.1%)	98 (25.6%)	0.043	0.013
Eye discharge	5 (1.3%)	7 (1.8%)	15 (3.9%)	0.043	0.025

with the treatment groups. There was only a 0.8% incidence of somnolence with brimonidine-Purite 0.15% compared with 2.6% in brimonidine-Purite 0.2% and brimonidine 0.2%. Although this difference did not meet statistical significance, because it is a rare adverse event it could be clinically relevant.

Table 2 also shows a direct comparison of the adverse events between the subjects on brimonidine-Purite 0.15% and brimonidine 0.2%. This pairwise comparison showed a statistically significant difference favoring brimonidine-Purite 0.15% ($P < 0.001$) in overall incidence of adverse events. Statistically significant lower incidences of conjunctival hyperemia, allergic conjunctivitis, and oral dryness were shown in the brimonidine-Purite 0.15% group ($P \leq 0.013$).

There were no statistical differences in the visual acuity, cup/disc ratio, visual fields, heart rate, and systolic and diastolic blood pressure.

Quality of Life

There were no statistical differences in the investigators' response to the clinical success of the medications. However, there were significant differences in how patients rated their satisfaction with their study medication at the time of exit from the study. The level of satisfaction was greater for patients using brimonidine-Purite 0.15% than those using brimonidine 0.2% ($P = 0.005$) (Fig. 2). Although less statistically significant, the level of satisfaction was greater for patients using brimonidine-Purite 0.2% than those using brimonidine 0.2% ($P = 0.020$). There was no statistical difference between the level of satisfaction of patients using brimonidine-Purite 0.15% compared with those using brimonidine-Purite 0.2%.

Throughout the year, more than 90% of all the treatment groups rated their study medications as comfortable, very comfortable, or soothing (Fig. 3). However, there were significant differences in how patients rated the comfort of their study medication at the time of exit from the study. Significantly more patients reported that brimonidine-Purite 0.15% was more comfortable than brimonidine 0.2% ($P = 0.042$). Furthermore, patients reported that brimonidine-Purite 0.2% was more comfortable than brimonidine 0.2% ($P = 0.027$). There was no statistical significance between the level of comfort of patients using brimonidine-Purite 0.15% compared with those using brimonidine-Purite 0.2%.

Patient Discontinuations

The most frequent reasons cited for discontinuation (in descending order) were adverse events, lack of efficacy, administrative issues, and protocol violations. Lack of efficacy was cited as the reason for discontinuation in only 5.3% of these patients in all 3 groups.

There were no statistical differences among the groups regarding adverse events that led to discontinuation from the study ($P = 0.203$). A smaller percentage of patients, however, discontinued therapy in the brimonidine-Purite

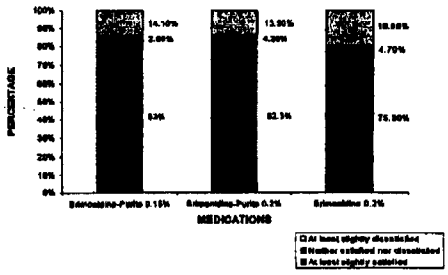


FIG. 3. Patient satisfaction evaluation summary for patients with glaucoma or ocular hypertension during 12-month treatment with brimonidine-Purite 0.15%, brimonidine-Purite 0.2%, and brimonidine 0.2%. The among-group P of 0.010 is a comparison of the seven-category response distributions for the three treatment groups. Patients rated the level of satisfaction with their study medication at the time of exit from the study. The pairwise comparison of brimonidine-Purite 0.15% versus brimonidine 0.2% yielded a P of 0.005, favoring brimonidine-Purite 0.15%.

0.15% (21.8%) group than in the brimonidine-Purite-0.2% (24.8%) or brimonidine-0.2% (27.4%) groups. The most common adverse events leading to discontinuation were conjunctival hyperemia, allergic conjunctivitis, and eye pruritus. Indeed, 5.1% fewer patients in brimonidine-Purite 0.15% cited allergic conjunctivitis as reason for discontinuation compared to brimonidine 0.2% (P = 0.017).

DISCUSSION

In this pooled analysis of two identically designed, 12-month, randomized, multisite, double-masked, parallel-group studies, brimonidine-Purite 0.15% and 0.2% provided IOP lowering comparable with brimonidine 0.2% in patients with glaucoma or ocular hypertension. Overall, the new 0.15% concentration of the brimonidine-Purite formulation showed IOP efficacy clinically comparable with brimonidine 0.2% throughout this 1-year study.

The formulations were applied three times daily in this study. The mean IOP at trough (8-AM measurement, before morning drop) of all 3 groups was comparable to the mean IOP at trough in previous studies where brimonidine 0.2% was administered twice daily[2–4] In an earlier study, application of brimonidine 0.2% three times daily and twice daily provided comparable IOP lowering at morning trough.[24] This finding suggests that brimonidine-Purite 0.15% would have comparable efficacy on morning IOP whether applied twice daily or three times daily; this hypothesis is being tested in an ongoing clinical trial.

Brimonidine 0.2%, which has been marketed since 1996, has shown a favorable adverse event profile, except for allergic conjunctivitis. The incidence of allergic conjunctivitis with brimonidine 0.2% has been reported to be 12.7% with twice-daily dosing.[4] In this present study, the incidence of allergic conjunctivitis was 15.7% for patients taking brimonidine 0.2% three times daily The higher incidence of allergic conjunctivitis is likely related to the increased frequency of dosing. It is interesting that the incidence of allergic conjunctivitis with patients on brimonidine-Purite 0.15% three times daily, which contains 25% less active ingredient of brimonidine, was only 9.2%. This incidence rate is less than the 12.7% incidence rate previously reported. This finding strongly suggests that with a twice-daily dosing of brimonidine-Purite 0.15%, the incidence of allergic conjunctivitis may be even lower than the 9.2% incidence with three-times-daily dosage regimen. Furthermore, it appears that the decreased concentration of brimonidine is primarily responsible for the decreased incidence of allergic conjunctivitis. The relative percent difference in allergic conjunctivitis during this current 1-year study was at least 41% less with brimonidine-Purite 0.15% than with brimonidine-Purite 0.2% or brimonidine 0.2%. Brimonidine-Purite 0.15% also had a significantly lower incidence of oral dryness than brimonidine 0.2%. Although not statistically significant, the lower incidence of somnolence with brimonidine-Purite 0.15% could prove to be beneficial. These findings suggest that brimonidine-Purite 0.15% has a superior adverse-events profile compared with brimonidine 0.2%.

In addition to having a comparable IOP-lowering effect to brimonidine 0.2% solution and a superior adverse event profile, reformulated brimonidine-Purite 0.15% appears to be better tolerated than brimonidine 0.2%. Brimonidine-Purite 0.15% had a significantly higher rate of satisfaction (P = 0.005) and comfort (P = 0.042) than the original formulation (Figs. 2 and 3). At the patients' last visit, more than 80% were satisfied with the reformulated brimonidine-Purite 0.15%, and 84.6% (P = 0.042) found it to be comfortable. The higher comfort experienced by those in the brimonidine-Purite groups should lead to improved compliance with the antiglaucoma regimen. The potentially enhanced ocular bioavailability associated with the reformulation may also explain why brimonidine-Purite 0.15% shows efficacy comparable with brimonidine 0.2% with a lower concentration of active drug (Fig. 4).

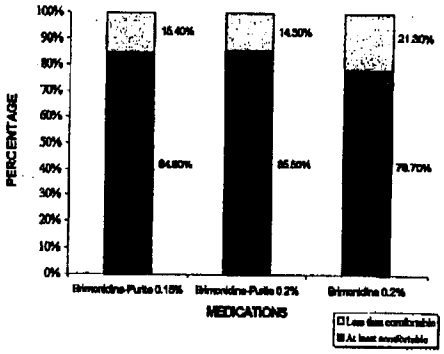


FIG. 4. Patient comfort evaluation summary for patients with glaucoma or ocular hypertension during 12-month treatment with brimonidine-Purite 0.15%, brimonidine-Purite 0.2%, and brimonidine 0.2%. The among-group P of 0.049 is a comparison of the six-category response distributions for the three treatment groups. Patients rated the level of satisfaction with their study medication at the time of exit from the study. The pairwise comparison of brimonidine-Purite 0.15% versus brimonidine 0.2% yielded a P of 0.042, favoring brimonidine-Purite 0.15%.

CONCLUSIONS

Brimonidine-Purite at concentrations of 0.15% or 0.2% effectively lowers IOP in patients with glaucoma or ocular hypertension. Brimonidine-Purite 0.15% also shows comparable efficacy with brimonidine 0.2% with less than a 1-mm Hg difference between study drugs at all time points throughout this study. The brimonidine-Purite 0.15% concentration showed a more favorable safety and tolerability profile with a 41% relative percent reduction in ocular allergy when compared with brimonidine 0.2%. The brimonidine-Purite 0.15% formulation received superior satisfaction and comfort ratings. Based on these clinical findings, it can be concluded that brimonidine-Purite 0.15% is an effective, safe, and well-tolerated therapy for the long-term treatment of high IOP.

APPENDIX

Members of the Brimonidine-Purite Study Groups 1 and 2 investigators include (in alphabetical order) Mark Abelson, MD, Edward Andersen, MD, Amy Batoosingh BA, Richard S. Bennion, MD, E. Randy Craven, MD, Harvey DuBiner, MD, Richard Evans, MD, Carlos Felix, MS, William C. Flynn, MD, Daniel Foreman, MD, Gary N. Foulks, MD, Stephen Gee, MD, L. Jay Katz, MD, Alex Kent, MD, Jeff Lozier, MD, Jeffrey Morris, MD, Thomas Mundorf, MD, Charles S. Ostrov, MD, Matthew Parsons, MD, Jay Perlman, MD, PhD, Michael J. Price, MD, Arnold Prywes, MD, Edward R. Rashid, MD, Patrick Riedel, MD, Elenora Safyan, BS, Kenneth Sall, MD, John Samples, MD, Thomas Samuelson, MD, Howard I. Schenker, MD, Gail Schwartz, MD, PA, John D. Sheppard, MD, Dong H. Shin, MD, PhD, Steven Simmons, MD, Dara Stevenson, MD, William C. Stewart, MD, Richard T. Sturm, MD, Lloyd Suter, MD, Stuart A. Terry, MD, Christopher M. Tortora, MD, Thomas R. Walters, MD, Mark Weiss, MD, Sidney Weiss, MD, Robert D. Williams, MD, Lisa Wohl, MD, SC, Eugene Barry Wolchok, MD, and Brandon Wool, MD.

REFERENCES

1. Melamed A, David R. Ongoing clinical assessment of the safety profile and efficacy of brimonidine compared with timolol: year-three results. *Clin Ther* 2000;22:103–11.
2. Schuman JS. Clinical experience with brimonidine 0.2% and timolol 0.5% in glaucoma and ocular hypertension. *Surv Ophthalmol* 1996;41(Suppl 1):S27–37.
3. LeBlanc RP. 12-month results of an ongoing randomized trial comparing brimonidine tartrate 0.2% and timolol 0.5% given twice daily in glaucoma or ocular hypertension. *Ophthalmology* 1998; 105:1960–7.
4. Katz LJ, for the Brimonidine Study Groups 1 and 2. Twice-daily brimonidine tartrate 0.2% vs timolol 0.5%: 1-year results in glaucoma patients. *Am J Ophthalmol* 1999;127:20–6.
5. Schuman JS. Effects of systemic β-blocker therapy on the efficacy and safety of topical brimonidine and timolol. *Ophthalmology* 2000;107:1171–7.
6. Cantor LB. The evolving pharmacotherapeutic profile of brimonidine, an α_2-adrenergic agonist, after four years of continuous use. *Exp Opin Pharmacother* 2000;1:815–34.
7. Schuman JS, Horwitz B, Choplin NT, et al. A one-year study of brimonidine twice daily in glaucoma and ocular hypertension. A controlled, randomized, multicenter clinical trial. Chronic Brimonidine Study Group. *Arch Ophthalmol* 1997;115:847–52.
8. Lee DA. Efficacy of brimonidine as replacement therapy in patients with open-angle glaucoma or ocular hypertension. *Clin Ther* 2000;22:53–65.
9. Lee DA, Gornbein J, Abrams C. The effectiveness and safety of brimonidine as mono-, combination, or replacement therapy for patients with primary open-angle glaucoma or ocular hypertension: a post hoc analysis of an open-label community trial. *J Ocul Pharmacother* 2000;16:3–18.
10. Serle JB. A comparison of the safety and efficacy of twice daily brimonidine 0.2% versus betaxolol 0.25% in subjects with elevated intraocular pressure. *Surv Ophthalmol* 1996;41(Suppl 1):S39–47.
11. Javitt J, Goldberg I. Comparison of the clinical success rates and quality of life effects of brimonidine tartrate 0.2% and betaxolol 0.25% suspension in patients with open-angle glaucoma and ocular hypertension. *J Glaucoma* 2000;9:398–408.
12. Robin AL. Questions concerning the role of apraclonidine in the management of glaucoma. *Arch Ophthalmol* 1995;113;712–4.
13. Abelson MB, Chapin M, Batoosingh A, et al. A retrospective examination of drug-induced allergy to Alphagan and a proposal for a new reporting system. *Invest Ophthalmol Vis Sci* 1999;40: S515, (abstract 2718).
14. Berdy GJ, Abelson MB, Smith LM, George MA. Preservative-free artificial tear preparations. Assessment of corneal epithelial toxic effects. *Arch Ophthalmol* 1992;110:528–532.
15. Pisella PJ, Fillacier K, Elena PP, et al. Comparison of the effects of preserved and unpreserved formulations of timolol on the ocular surface of albino rabbits. *Ophthalmic Res* 2000;32:3–8.
16. Gasset AR, Ishii Y, Kaufman HE, Miller T. Cytotoxicity of ophthalmic preservatives. *Am J Ophthalmol* 1974;78:98–105.
17. De Saint Jean M, Debbasch C, et al. Toxicity of preserved and unpreserved antiglaucoma topical drugs in an in vitro model of conjunctival cells. *Curr Eye Res* 2000;20:85–94.
18. Grant WM, Schuman JS. *Toxicology of the Eye.* 4th ed. Springfield, IL: CC Thomas, 1990:208–13.
19. Debbasch C, Rat P, Warner J-M. Evaluation of the toxicity of benzalkonium chloride on the ocular surface. *J Toxicol Cutaneous Ocul Toxicol* 2000;19(2–3):105–115.
20. Rozen S, M. Abelson, A. Giovanoni, D. Welch. Assessment of the comfort and tolerance of 0.5% carboxymethylcellulose preserved with Purite (Refresh Tears) in dry eye sufferers [Abstract]. *Invest Ophthalmol Vis Sci* 1998;39:B343.
21. Masschelein WJ. *Chlorine Dioxide, Chemistry and Environmental Impact of Oxychlorine Compounds.* Ann Arbor, MI: Ann Arbor Science, 1979.
22. Grant R, Ajello M, Vlass E. Salt water or high tech? A look at two new rinsing solutions for contact lenses. *Optician* 1996;212:38–41.
23. Data on file, Allergan. Department of Pharmacokinetics and Drug Metabolism. 1999.
24. Rosenthal AL, Walters T, Berg E, Safyan E, Batoosingh AL. A comparison of the safety and efficacy of brimonidine 0.2%, BID versus TID, in subjects with elevated intraocular pressure. *Invest Ophthalmol Vis Sci* 1996;37(Suppl):S1102, (abstract).
25. Walters RT. Development and use of brimonidine in treating acute and chronic elevations of intraocular pressure: a review of safety, efficacy, dose response, and dosing studies. *Surv Ophthalmol* 1996;41(Suppl 1):S19–26.

RECEIVED
MAR 28 2003
TECH CENTER 1600/2900

PATENT & TRADEMARK OFFICE
MAR 24 2003

DOCKET NO. 1756 (AP) PA[illegible]

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of Olejnik et al	Group Art Unit: 1615
Serial No: 10/236,566	Examiner: Bennett, R.
Filed: September 6, 2002	
For: COMPOSITIONS CONTAINING ALPHA-2-AGONIST ADRENERGIC AGONIST COMPONENTS	

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 first issuing on co-pending United States Patent Application No. 09/904,018. 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. 09/904,018, 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

03/27/2003 CW0111 00000052 010885 10236566
01 FC:1814 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: 3/14/03

By: Carlos A. Fisher

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

DOCKET NO. 17361CON(AP)
PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of Olejnik et al	Group Art Unit: 1615
Serial No: 10/236,566	Examiner: Bennett, R.
Filed: September 6, 2002	
For: COMPOSITIONS CONTAINING ALPHA-2-AGONIST ADRENERGIC AGONIST COMPONENTS	

Commissioner of Patents
Washington, D.C. 20231

TERMINAL DISCLAIMER TO OBVIATE A PROVISIONAL DOUBLE PATENTING REJECTION OVER BOTH AN ISSUED PATENT AND A PENDING PATENT APPLICATION

Dear Sir:

The owner, ALLERGAN SALES, LLC, successor by operation of law to 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 1) any patent issuing on co-pending United States Patent Application No. 09/904,018 and on 2) issued United States Patent 6,562,873. The owner hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it, any patent issuing from the above- identified patent application, and the above-identified patent are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors or assigns.

05/22/2003 MAHY22 0006905 010885 10236566
01 FC:1814 110.00 CH

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 either 1) any patent issuing from United States Patent Application No. 09/904,018, or 2) issued United States Patent 6,562,873 as presently shortened by any terminal disclaimer, in the event that one

Received from <+17142484249> at 5/19/03 6:02:06 PM [Eastern Daylight Time]

or both of the latter: 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 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: 5/19/03

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

ALLERGAN SALES, LLC

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

FACSIMILE TRANSMISSION

The information contained in this transmission is privileged and confidential. It is intended only for the use of the individual or entity named below. If the reader of this message is not the intended recipient or the employee or agent responsible for delivering the message to the intended recipient, you are hereby notified that any dissemination, distribution, or copying of this communication is strictly prohibited.

If you have received this communication in error, please notify Allergan immediately by telephone and return the original message to us at the below-indicated address via regular U.S. mail. Thank you.

FROM: Carlos A. Fisher
2525 Dupont Drive
Irvine, California 92612

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

TO: Group 1615
R. Bennett
U.S. Patent & Trademark Office

Facsimile No.: 703-746-5315

*Number of pages (including this cover page): 3

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

---

In re: Olejnik, et al.

Appln. No.: 10/236,566

Filed: September 6, 2002

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

Docket No. 17361CON(AP)

Date: May 19, 2003

Name or type of papers being transmitted:

1) Facsimile Transmission Sheet
2) Terminal Disclaimer

CERTIFICATE OF FACSIMILE TRANSMISSION

I hereby certify that this paper is being facsimile transmitted to the United States Patent and Trademark Office on the date shown below to (703) 746-5315.

Date: 5/19/2003

By: Bonnie Ferguson
BONNIE FERGUSON

FACSIMILE TRANSMISSION

The information contained in this transmission is privileged and confidential. It is intended only for the use of the individual or entity named below. If the reader of this message is not the intended recipient or the employee or agent responsible for delivering the message to the intended recipient, you are hereby notified that any dissemination, distribution, or copying of this communication is strictly prohibited.

If you have received this communication in error, please notify Allergan immediately by telephone and return the original message to us at the below-indicated address via regular U.S. mail. Thank you.

FROM: Carlos A. Fisher
2525 Dupont Drive
Irvine, California 92612

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

TO: Group 1615
R. Bennett
U.S. Patent & Trademark Office

Facsimile No.: 703-746-5315

*Number of pages (including this cover page): 3

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

---

In re: Olejnik, et al.

Appln. No.: 10/236,566

Filed: September 6, 2002

Docket No. 17361CON(AP)

Date: May 19, 2003

Title: COMPOSITIONS CONTAINING ALPHA-2 AGONIST ADRENERGIC AGONIST COMPONENTS

Name or type of papers being transmitted:

1) Facsimile Transmission Sheet
2) Terminal Disclaimer

CERTIFICATE OF FACSIMILE TRANSMISSION

I hereby certify that this paper is being facsimile transmitted to the United States Patent and Trademark Office on the date shown below to (703) 746-5315.

Date: 5/19/2003

By: Bonnie Ferguson

Received from <+17142464249> at 5/19/03 6:02:08 PM [Eastern Daylight Time]

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

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

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

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

Date of Interview: *May 19 & 21, 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: *on record*.

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 and examiner agreed to cancel claims 52 and 62. Claims 47 and 57 would be amended to "about" 21 deg C. Support for the amendment is found on page 30, line 22 of the specification*.

(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 M. Bennett
Examiner's signature, if required

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

U.S. Patent and Trademark Office
PTO-413 (Rev. 04-03) Interview Summary Paper No. 18

mmary of Record of Interview Requireme

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

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

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

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

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

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

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

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

It is desirable that the examiner orally remind the applicant of his or her obligation to record the substance of the interview of each case. It should be noted, however, that the Interview Summary Form will not normally be considered a complete and proper recordation of the interview unless it includes, or is supplemented by the applicant or the examiner to include, all of the applicable items required below concerning the substance of the interview.

A complete and proper recordation of the substance of any interview should include at least the following applicable items:
1) A brief description of the nature of any exhibit shown or any demonstration conducted,
2) an identification of the claims discussed,
3) an identification of the specific prior art discussed,
4) an identification of the principal proposed amendments of a substantive nature discussed, unless these are already described on the Interview Summary Form completed by the Examiner,
5) a brief identification of the general thrust of the principal arguments presented to the examiner,
(The identification of arguments need not be lengthy or elaborate. A verbatim or highly detailed description of the arguments is not required. The identification of the arguments is sufficient if the general nature or thrust of the principal arguments made to the examiner can be understood in the context of the application file. Of course, the applicant may desire to emphasize and fully describe those arguments which he or she feels were or might be persuasive to the examiner.)
6) a general indication of any other pertinent matters discussed, and
7) if appropriate, the general results or outcome of the interview unless already described in the Interview Summary Form completed by the examiner.

Examiners are expected to carefully review the applicant's record of the substance of an interview. If the record is not complete and accurate, the examiner will give the applicant an extendable one month time period to correct the record.

Examiner to Check for Accuracy

If the claims are allowable for other reasons of record, the examiner should send a letter setting forth the examiner's version of the statement attributed to him or her. If the record is complete and accurate, the examiner should place the indication, "Interview Record OK" on the paper recording the substance of the interview along with the date and the examiner's initials.

Notice of Allowability	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--

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

1. ☒ This communication is responsive to *Amendment B filed 3/24/03 and Terminal Disclaimer filed 5/19/03*.
2. ☒ The allowed claim(s) is/are *47-51,53-61 and 63-70*.
3. ☒ The drawings filed on *9/6/02* are accepted by the Examiner.
4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
   a) ☐ All b) ☐ Some* c) ☐ None of the:
      1. ☐ Certified copies of the priority documents have been received.
      2. ☐ Certified copies of the priority documents have been received in Application No. _____.
      3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.
5. ☒ 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.
6. ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

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

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

8. ☐ CORRECTED DRAWINGS must be submitted.
   (a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review (PTO-948) attached
      1) ☐ hereto or 2) ☐ to Paper No. ____.
   (b) ☐ including changes required by the proposed drawing correction filed _____, which has been approved by the Examiner.
   (c) ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No. _____.

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet.

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

Attachment(s)

1☐ Notice of References Cited (PTO-892)
2☐ Notice of Informal Patent Application (PTO-152)
3☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
4☒ Interview Summary (PTO-413), Paper No. *10*.
5☐ Information Disclosure Statements (PTO-1449), Paper No. ____.
6☒ Examiner's Amendment/Comment
7☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
8☐ Examiner's Statement of Reasons for Allowance
9☐ Other

THURMAN K. PAGE
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

DETAILED ACTION

The examiner acknowledges receipt of Amendment B filed 3/24/03.

Terminal Disclaimer

1. The terminal disclaimer filed on 5/19/03 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of US Patent Application 09/904,018 or US Patent 6,562,873 has been reviewed and is accepted. The terminal disclaimer has been recorded.

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

Authorization for this examiner's amendment was given in a telephone interview with Carlos Fisher on May 19, 2003.

The application has been amended as follows:

Please cancel claims 52 and 62.

Please amend claim 47, line 4, insert "about" before "21°C".

Please amend claim 57, line 6, insert "about" before "21°C".

Allowable Subject Matter

3. Claims 47-51, 53-61, 63-70 are allowed.

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
May 23, 2003

THURMAN K. PAGE
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

UNITED STATES PATENT AND TRADEMARK OFFICE

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

NOTICE OF ALLOWANCE AND FEE(S) DUE

33197 7590 06/03/2003

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

EXAMINER	
BENNETT, RACHEL M	
ART UNIT	CLASS-SUBCLASS
1615	424-427000

DATE MAILED: 06/03/2003

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

TITLE OF INVENTION: COMPOSITIONS CONTAINING ALPHA-2-ADRENERGIC AGONIST COMPONENTS

APPLN. TYPE	SMALL ENTITY	ISSUE FEE	PUBLICATION FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	NO	$1300	$300	$1600	09/03/2003

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

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE REFLECTS A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE APPLIED IN THIS APPLICATION. THE PTOL-85B (OR AN EQUIVALENT) MUST BE RETURNED WITHIN THIS PERIOD EVEN IF NO FEE IS DUE OR THE APPLICATION WILL BE REGARDED AS ABANDONED.

HOW TO REPLY TO THIS NOTICE:

I. Review the SMALL ENTITY status shown above.

If the SMALL ENTITY is shown as YES, verify your current SMALL ENTITY status:
A. If the status is the same, pay the TOTAL FEE(S) DUE shown above.

B. If the status is changed, pay the PUBLICATION FEE (if required) and twice the amount of the ISSUE FEE shown above and notify the United States Patent and Trademark Office of the change in status, or

If the SMALL ENTITY is shown as NO:

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

B. If applicant claimed SMALL ENTITY status before, or is now claiming SMALL ENTITY status, check the box below and enclose the PUBLICATION FEE and 1/2 the ISSUE FEE shown above.

☐ Applicant claims SMALL ENTITY status. See 37 CFR 1.27.

II. PART B - FEE(S) TRANSMITTAL should be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). Even if the fee(s) have already been paid, Part B - Fee(s) Transmittal should be completed and returned. If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted.

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

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

PTOL-85 (REV. 05-03) Approved for use through 04/30/2004.

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: **Mail** **Mail Stop ISSUE FEE**
Commissioner for Patents
Alexandria, Virginia 22313-1450
Fax **(703)746-4000**

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 4 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Legibly mark-up with any corrections or use Block 1)

33197 7590 06/03/2003

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

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

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

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

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

TITLE OF INVENTION: COMPOSITIONS CONTAINING ALPHA-2-ADRENERGIC AGONIST COMPONENTS

APPLN. TYPE	SMALL ENTITY	ISSUE FEE	PUBLICATION FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	NO	$1300	$300	$1600	09/03/2003

EXAMINER	ART UNIT	CLASS-SUBCLASS
BENNETT, RACHEL M	1615	424-427000

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

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

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

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

1 _____
2 _____
3 _____

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

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. Inclusion of assignee data is only appropriate when an assignment has been previously submitted to the USPTO or is being submitted under separate cover. Completion of this form is NOT a substitute for filing an assignment.

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

Please check the appropriate assignee category or categories (will not be printed on the patent) ☐ individual ☐ corporation or other private group entity ☐ government

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

☐ Issue Fee
☐ Publication Fee
☐ Advance Order - # of Copies _____

4b. Payment of Fee(s):

☐ A check in the amount of the fee(s) is enclosed.
☐ Payment by credit card. Form PTO-2038 is attached.
☐ The Commissioner is hereby authorized by charge the required fee(s), or credit any overpayment, to Deposit Account Number _____ (enclose an extra copy of this form).

Commissioner for Patents is requested to apply the Issue Fee and Publication Fee (if any) or to re-apply any previously paid issue fee to the application identified above.

(Authorized Signature) (Date)

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

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

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

TRANSMIT THIS FORM WITH FEE(S)

UNITED STATES PATENT AND TRADEMARK OFFICE

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

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

33197 7590 06/03/2003

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

EXAMINER	
BENNETT, RACHEL M	

ART UNIT	PAPER NUMBER
1615	

DATE MAILED: 06/03/2003

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

The patent term adjustment to date is 0 days. If the issue fee is paid on the date that is three months after the mailing date of this notice and the patent issues on the Tuesday before the date that is 28 weeks (six and a half months) after the mailing date of this notice, the term adjustment will be 0 days.

If a continued prosecution application (CPA) was filed in the above-identified application, the filing date that determines patent term adjustment is the filing date of the most recent CPA.

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

Any questions regarding the patent term extension or adjustment determination should be directed to the Office of Patent Legal Administration at (703)305-1383.

PTOL-85 (REV. 05-03) Approved for use through 04/30/2004.

UNITED STATES PATENT AND TRADEMARK OFFICE

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

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

33197 7590 06/03/2003

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

EXAMINER	
BENNETT, RACHEL M	
ART UNIT	**PAPER NUMBER**
1615	

DATE MAILED: 06/03/2003

Notice of Fee Increase on January 1, 2003

If a reply to a "Notice of Allowance and Fee(s) Due" is filed in the Office on or after January 1, 2003, then the amount due will be higher than that set forth in the "Notice of Allowance and Fee(s) Due" since there will be an increase in fees effective on January 1, 2003. See Revision of Patent and Trademark Fees for Fiscal Year 2003: Final Rule, 67 Fed. Reg. 70847, 70849 (November 27, 2002).

The current fee schedule is accessible from: http://www.uspto.gov/main/howtofees.htm.

If the issue fee paid is the amount shown on the "Notice of Allowance and Fee(s) Due," but not the correct amount in view of the fee increase, a "Notice to Pay Balance of Issue Fee" will be mailed to applicant. In order to avoid processing delays associated with mailing of a "Notice to Pay Balance of Issue Fee," if the response to the Notice of Allowance and Fee(s) due form is to be filed on or after January 1, 2003 (or mailed with a certificate of mailing on or after January 1, 2003), the issue fee paid should be the fee that is required at the time the fee is paid. If the issue fee was previously paid, and the response to the "Notice of Allowance and Fee(s) Due" includes a request to apply a previously-paid issue fee to the issue fee now due, then the difference between the issue fee amount at the time the response is filed and the previously paid issue fee should be paid. See Manual of Patent Examining Procedure, Section 1308.01 (Eighth Edition, August 2001).

Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at (703) 305-8283.

PTOL-85 (REV. 05-03) Approved for use through 04/30/2004.

JUN 11 2003 JC40 PATENT & TRADEMARK OFFICE

11:17AM FROM-Frank 8484901784 T-160 P.002/001 F-689

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: Mail Mail Stop ISSUE FEE
Commissioner for Patents
Alexandria, Virginia 22313-1450
Fax (703)746-4000

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

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

JANET MCGHEE (Typed or printed name)
Janet McGhee (Signature)
JUNE 11, 2003 (Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/236,566	09/06/2002	Dean Oliphant	D-2000CON	3779

TITLE OF INVENTION: COMPOSITIONS CONTAINING ALPHA-2-ADRENERGIC AGONIST COMPONENTS

APPLN. TYPE	SMALL ENTITY	ISSUE FEE	PUBLICATION FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	NO	$1300	$300	$1600	09/06/2003

EXAMINER	ART UNIT	CLASS-SUBCLASS
BENNETT, RACHEL M	1615	424-078000

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

2. For printing on the patent front page, list (1) the names of up to 3 registered patent attorneys or agents OR, alternatively, (2) the name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.
1 Stout, Uxa, Buyan & Mullins, LLP
2 Frank J. Uxa
3 Carlos A. Fisher

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)
PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. Inclusion of assignee data is only appropriate when an assignment has been previously submitted to the USPTO or is being submitted under separate cover. Completion of this form is NOT a substitute for filing an assignment.
(A) NAME OF ASSIGNEE: ALLERGAN SALES, INC.
(B) RESIDENCE: (CITY and STATE OR COUNTRY): IRVINE, CA

OK to Enter

Please check the appropriate assignee category or categories (will not be printed on the patent) ☐ individual ☒ corporation or other private group entity ☐ government

4a. The following fee(s) are enclosed:
☒ Issue Fee
☒ Publication Fee
☒ Advance Order - # of Copies 10

4b. Payment of Fee(s):
☐ A check in the amount of the fee(s) is enclosed.
☐ Payment by credit card. Form PTO-2038 is enclosed.
☒ The Commissioner is hereby authorized to charge the required fee(s), or credit any overpayment, to Deposit Account Number 01-0885

Commissioner for Patents is requested to apply the Issue Fee and Publication Fee (if any) or to re-apply any previously paid issue fee to the application identified above.

(Authorized Signature) (Date) 6/11/03

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

06/12/2003 HBENDAF2 00000088 010885 10236566
01 FC:1501 1300.00 CH
02 FC:1504 300.00 CH
03 FC:8001 30.00 CH

TRANSMIT THIS FORM WITH FEE(S)

PTOL-85 (REV. 05-03) Approved for use through 04/30/2004. OMB 0651-0033 U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Received from <8484901784> at 6/11/03 2:30:15 PM [Eastern Daylight Time]

JUN 11 11:17AM FROM-Frank 8484581784 T-168 P.003/003 F-858

OIPE JC40 JUN 11 2003 PATENT & TRADEMARK OFFICE

#12
9/29/03
DJF

PTO/SB/122 (10-01)
Approved for use through 10/31/2002. OMB 0651-0035
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

CHANGE OF CORRESPONDENCE ADDRESS
Application

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

Application Number	10/236,566 → 10/236,566
Filing Date	September 6, 2002
First Named Inventor	Osinik
Art Unit	1615
Examiner Name	Bennett, R.M.
Attorney Docket No.	D-2662 CON

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

☐ Customer Number _____ → _____
OR Customer Number Customer Number/Bar Code

☒ 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 714-246-4248

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: [signature]

Date: 6/11/03

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.

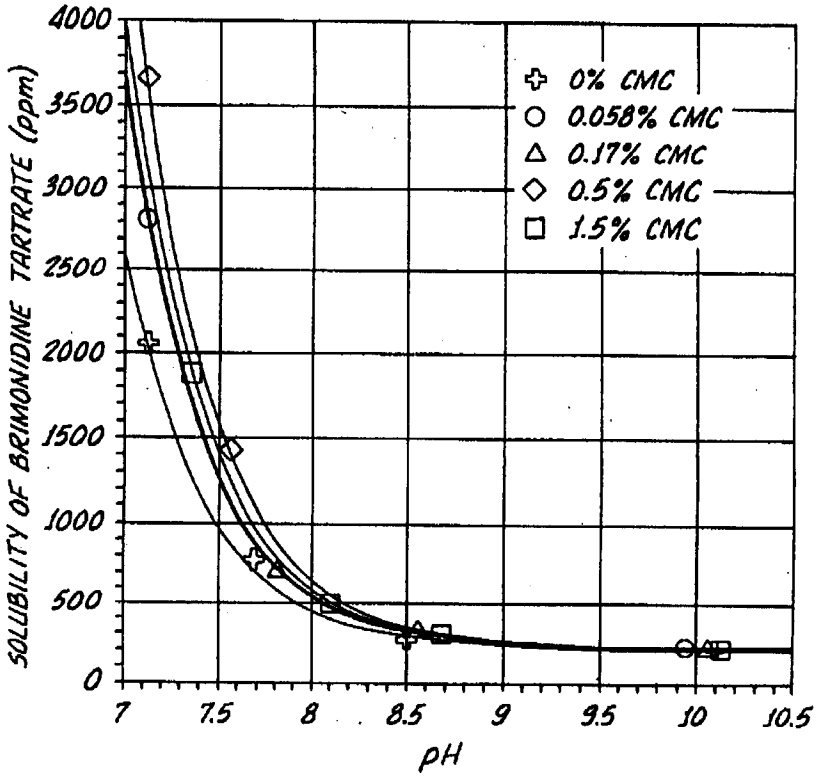
Received from <8484581784> at 6/11/03 2:30:15 PM [Eastern Daylight Time]

APPROVED BY DRAFTSMAN	O.G. FIG.	
	CLASS	SUBCLASS
	424	427

10236566.090602

1/1

6641834



PATENT APPLICATION FEE DETERMINATION RECORD
Effective October 1, 2001

Application or Docket Number: D-2892CON.

CLAIMS AS FILED - PART I

	(Column 1)	(Column 2)
TOTAL CLAIMS	20	
FOR	NUMBER FILED	NUMBER EXTRA
TOTAL CHARGEABLE CLAIMS	20 minus 20=	*0
INDEPENDENT CLAIMS	2 minus 3 =	*0
MULTIPLE DEPENDENT CLAIM PRESENT		☐

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

SMALL ENTITY TYPE ☐		OR	OTHER THAN SMALL ENTITY	
RATE	FEE		RATE	FEE
BASIC FEE	370.00	OR	BASIC FEE	740.00
X$ 9=		OR	X$18=	
X42=		OR	X84=	
+140=		OR	+280=	
TOTAL		OR	TOTAL	740.00

CLAIMS AS AMENDED - PART II

AMENDMENT A	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA
Total	*	Minus	**	=
Independent	*	Minus	***	=
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM				☐

SMALL ENTITY		OR	OTHER THAN SMALL ENTITY	
RATE	ADDITIONAL FEE		RATE	ADDITIONAL FEE
X$ 9=		OR	X$18=	
X42=		OR	X84=	
+140=		OR	+280=	
TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	

AMENDMENT B	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA
Total	*	Minus	**	=
Independent	*	Minus	***	=
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM				☐

RATE	ADDITIONAL FEE		RATE	ADDITIONAL FEE
X$ 9=		OR	X$18=	
X42=		OR	X84=	
+140=		OR	+280=	
TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	

AMENDMENT C	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA
Total	*	Minus	**	=
Independent	*	Minus	***	=
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM				☐

RATE	ADDITIONAL FEE		RATE	ADDITIONAL FEE
X$ 9=		OR	X$18=	
X42=		OR	X84=	
+140=		OR	+280=	
TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20."
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3."
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

FORM PTO-875 (Rev. 8/01) *U.S. Government Printing Office: 2001 -- 484-484/59268 Patent and Trademark Office, U.S. DEPARTMENT OF COMMERCE

CLAIMS ONLY

SERIAL NO.	FILING DATE
APPLICANT(S)	

CLAIMS

	AS FILED		AFTER 1st AMENDMENT		AFTER 2nd AMENDMENT	
	IND.	DEP.	IND.	DEP.	IND.	DEP.
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
13						
14						
15						
16						
17						
18						
19						
20						
21						
22						
23						
24						
25						
26						
27						
28						
29						
30						
31						
32						
33						
34						
35						
36						
37						
38						
39						
40						
41						
42						
43						
44						
45						
46						
47						
48						
49						
50						
TOTAL IND.						
TOTAL DEP.						
TOTAL CLAIMS						

	*		*		*	
	IND.	DEP.	IND.	DEP.	IND.	DEP.
51						
52						
53						
54						
55						
56						
57						
58						
59						
60						
61						
62						
63						
64						
65						
66						
67						
68						
69						
70						
71						
72						
73						
74						
75						
76						
77						
78						
79						
80						
81						
82						
83						
84						
85						
86						
87						
88						
89						
90						
91						
92						
93						
94						
95						
96						
97						
98						
99						
100						
TOTAL IND.	2					
TOTAL DEP.	18					
TOTAL CLAIMS	20					

*MAY BE USED FOR ADDITIONAL CLAIMS OR AMENDMENTS

FORM PTO-2022 (1-96)

U.S.DEPARTMENT OF COMMERCE
Patent and Trademark Office

*U.S. Government Printing Office: 1998 - 433-214/70303