CLINICAL REVIEW

Application Type	NDA 21-398
Submission Number	N-000
Submission Code	AZ
Letter Date	May 2, 2007
Stamp Date	May 3, 2007
PDUFA Goal Date	November 2, 2007
Reviewer Name	William M. Boyd, M.D.
Review Completion Date	September 19, 2007
Established Name	brimonidine tartrate-timolol maleate ophthalmic solution 0.2%/0.5%
(Proposed) Trade Name	Combigan
Therapeutic Class	alpha-agonist/beta-blocker
Applicant	Allergan, Inc.
Priority Designation	S
Formulation	ophthalmic solution
Dosing Regimen	one drop B.I.D.
Indication	reduction of elevated intraocular pressure in patients with glaucoma or ocular hypertension who require adjunctive or replacement therapy due to inadequately controlled IOP.
Intended Population	patients with ocular hypertension or [redacted] glaucoma

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

NDA 21-398 for Combigan (brimonidine tartrate/timolol maleate ophthalmic solution) 0.2%/0.5% is recommended for approval with the labeling revisions found in this review; the IOP-lowering of Combigan BID was less than that seen with the concomitant administration of 0.5% timolol BID and 0.2% brimonidine TID, but the safety profile was improved.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

There are no proposed risk management actions except the usual postmarketing collection and reporting of adverse experiences associated with the use of the drug product.

1.2.2 Required Phase 4 Commitments

There are no recommended Phase 4 clinical study commitments.

1.2.3 Other Phase 4 Requests

There are no optional or recommended Phase 4 requests.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

The data contained in the original NDA, in an amendment dated September 13, 2004, and in an amendment dated June 29, 2006, did not adequately show that each component made a contribution to the claimed effect of the combination product.

An alternative dosing regimen could provide a useful product if it could be demonstrated that the safety profile of the proposed combination product is better than that of the individual agents taken as currently permitted in the approved labeling; the combination's IOP-lowering ability is inferior (approximately 1-2 mmHg) to that of brimonidine and timolol given concomitantly.

Post-hoc analysis of the pooled phase 3 studies 012T/013T, patients receiving combination BID had a significantly lower incidence of somnolence than patients receiving brimonidine TID.

The Agency did not accept these post-hoc analyses, but they did serve to generate the hypothesis that the safety profile of the proposed combination product is better than that of the individual agents taken as currently permitted in the approved labeling for somnolence. Sleepiness is associated with decreased reaction time and impaired cognitive performance, and the effect on vehicular crashes resulting in injury and death is well established. A study conducted by Connor et al (2002)[1] showed that an SSS score in the 4 to 7 range confers an 8-fold increased risk of a serious car crash over scores in the 1 to 3 range (odds ratio = 8.2).

Study 190342-023T was designed to address this hypothesis by evaluating and comparing the safety of fixed combination BID with 0.2% Alphagan TID and 0.5% timolol BID given concurrently following ocular administration for 10 days in healthy, adult subjects.

Although Study 190342-023T demonstrated that the safety profile of the proposed combination product was numerically superior to the individual agents taken as currently permitted in their approved labeling in the incidence of oral dryness adverse events, this difference in adverse events was not sufficient to offset the combination's inferior IOP-lowering ability (approximately 1-2 mmHg) compared to that of brimonidine and timolol given concomitantly. It would have greatly boosted Allergan's claim that the safety profile of the proposed combination product is significantly better than that of the individual agents taken as currently permitted in their approved labeling had the proportion of sleepiness responders been demonstrated as statistically and clinically significant.

After review of the statistical analysis plan for study 023T, the Agency suggested that Allergan consider examining the effect of age on these adverse events. In response, Allergan reanalyzed the adverse event of sleepiness in the older subset of subjects in the -023T trial. In subjects ≥ 40 years old, the proportion of current severity of sleepiness responders was 16.0% (8/50) with Combination and 37.0% (17/46) with Concurrent, $p = 0.019$.

From the December 20, 2006, approvable letter:

> The Agency considers that there is preliminary evidence that the proposed combination has an improved safety profile in subjects over the age of 40. To confirm this hypothesis, a new trial similar to 190343-023T in a population of subjects whose age ≥ 40 is recommended; both the dry mouth and sleepiness endpoints would be expected to show significance and the magnitude would be expected to be at least that observed in the patients ≥ 40 years old in study 190343- 023T.

Study 190342-024T submitted in this May 2, 2007, amendment was designed to address this deficiency by evaluating and comparing the safety of fixed combination BID with 0.2% Alphagan TID and 0.5% timolol BID given concurrently following ocular administration for 10 days in glaucoma and ocular hypertension patients.

[1] Connor J, Norton R, Ameratunga S, et al. Driver sleepiness and risk of serious injury to car occupants: population based case control study. BMJ 2002;324:11-25.

1.3.2 Efficacy

No efficacy measurements were performed during study 190342-024T.

There is no new information submitted to alter the conclusion from the original NDA M.O. review:

- There are statistically significant differences in IOP at baseline between the combination and timolol in study 190342-012T.
- Neither study 190342-012T nor 190342-013T demonstrates a clinically significant contribution of brimonidine tartrate 0.2% to the combination product.
- There is a reproducible loss of IOP lowering ability of the combination versus brimonidine tartrate 0.2% seen in both phase 3 studies at hour 9 during each diurnal measurement.
- Neither study 190342-012T nor 190342-013T demonstrates a clinically significant contribution of timolol 0.5% to the combination product.

There is no new information submitted to alter the conclusion from the review of the September 13, 2004, M.O. review:

- Study 190342-019T fails to demonstrate that the efficacy of the combination product is equivalent to the efficacy attained when each of the individual components are dosed concurrently.

1.3.3 Safety

By finding a significant between-group difference in the current severity of Sleepiness Responders (a clinically relevant endpoint associated with decreased reaction time and impaired cognitive performance), Allergan has demonstrated that the fixed combination, alternative dosing regimen would provide a useful product because the safety profile of the proposed combination product is better than that of the individual agents taken as currently permitted in the approved labeling. The combination's IOP-lowering ability is, however, inferior (approximately 1-2 mmHg) to that of brimonidine and timolol given concomitantly.

The submitted studies in NDA 21-398 otherwise demonstrate no new, clinically relevant safety findings with the use of brimonidine tartrate 0.2%/timolol 0.5% ophthalmic solution in lowering intraocular pressure in patients with [redacted] glaucoma or ocular hypertension versus individual monotherapies.

1.3.4 Dosing Regimen and Administration

There is no recommendation for changing the dosing regimen for the combination product. See section 1.3.2 for dosing considerations.

1.3.5 Drug-Drug Interactions

Drug-drug interactions were not evaluated in this submission. There are theoretical reactions per the individual labels for brimonidine and timolol which are addressed in the revised labeling:

- Antihypertensives/Cardiac glycosides
- Beta-adrenergic blocking agents
- Calcium antagonists
- Catecholamine-depleting drugs
- CNS Depressants
- CYP2D6 inhibitors
- Tricyclic Antidepressants.

1.3.6 Special Populations

An evaluation of this use of this product in special populations was conducted in the original NDA review. There were no significant differences seen in the IOP lowering ability of the combination product in any of the subgroups analyzed. There were no gender, age or race effects on safety or efficacy with the use of the combination product.

2 INTRODUCTION AND BACKGROUND

Product information, currently available treatments for this indication, availability of proposed active ingredient in the United States, important issues with pharmacologically related products, presubmission regulatory activity, and relevant background information are located in the review of the original NDA submission.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

Not applicable to this amendment. There are no remaining issues. See previous CMC reviews for this NDA.

The submitted label has been reviewed by CMC and appropriate changes incorporated.

3.2 Animal Pharmacology/Toxicology

Not applicable to this amendment. There are no remaining issues. See previous Pharmacology/Toxicology reviews for this NDA.

The submitted label has been reviewed by Pharmacology/Toxicology and appropriate changes incorporated.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

Sources of clinical data utilized in this review include all the previously submitted/currently submitted trials conducted by the applicant as found in the following List of Clinical Studies in Section 4.2 of this review.

4.2 Tables of Clinical Studies

From the September 19, 2002, submission:

Protocol Type	Study Design	Treatment Duration	Patient Population	Treatment Groups	Dosing	#Pts enrolled/completed
190342-012T Phase 3 Safety and Efficacy	Multicenter, randomized, double masked, parallel, active control	3 months (plus 9-month masked extension)	Open angle glaucoma and ocular hypertension	brimonidine tartrate 0.2%/ timolol 0.5% brimonidine tartrate 0.2% timolol 0.5%	1gtt BID [a] 1 gtt TID 1 gtt BID [a]	573/497
190342-013T Phase 3 Safety and Efficacy	Multicenter, randomized, double masked, parallel, active control	3 months (plus 9-month masked extension)	Open angle glaucoma and ocular hypertension	brimonidine tartrate 0.2%/ timolol 0.5% brimonidine tartrate 0.2% timolol 0.5%	1gtt BID [a] 1 gtt TID 1 gtt BID [a]	586/502

[a] active drug administered in the morning and evening with masked vehicle administered in the afternoon

From the September 13, 2004, submission:

Protocol Type	Study Design	Treatment Duration	Patient Population	Treatment Groups	Dosing	#Pts enrolled/completed
190342-019T Phase 3 Concurrent versus concomitant therapy	Multicenter, randomized, double masked, parallel, active control	4 weeks	Open angle glaucoma and ocular hypertension	brimonidine tartrate 0.2%/ timolol 0.5% brimonidine tartrate 0.2% brimonidine tartrate 0.2% + timolol 0.5%	1gtt BID [1] 1 gtt TID [2] 1 gtt TID 1 gtt BID	432/403

[1]masked vehicle administered TID (morning, afternoon, and evening)
[2]masked vehicle was administered BID (morning and evening)

From the June 29, 2006, submission:

Protocol Type	Study Design	Treatment Duration	Patient Population	Treatment Groups	Dosing	#Pts enrolled/completed
190342-023T Phase 3 Safety	Multicenter, randomized, double masked, parallel, active control	10 days	Healthy subjects	brimonidine tartrate 0.2%/ timolol 0.5% brimonidine tartrate 0.2% + timolol 0.5%	1gtt BID [1] 1 gtt TID 1 gtt BID	452/441

[1]masked vehicle administered TID (morning, afternoon, and evening)

From the May 2, 2007, submission:

Protocol Type	Study Design	Treatment Duration	Patient Population	Treatment Groups	Dosing	#Pts enrolled/completed
190342-024T Phase 3 Safety	Multicenter, randomized, double masked, parallel, active control	10 days	Open angle glaucoma and ocular hypertension	brimonidine tartrate 0.2%/ timolol 0.5% brimonidine tartrate 0.2% + timolol 0.5%	1gtt BID [1] 1 gtt TID 1 gtt BID	604/590

[1]masked vehicle administered TID (morning, afternoon, and evening

4.3 Review Strategy

The May 2, 2007, submission was submitted electronically. All subsequent amendments were submitted electronically. All study reports were reviewed. The included clinical study report and all previously submitted study reports (see Section 4.2) formed the basis for the review of safety for the proposed indication.

A literature search conducted by this reviewer failed to identify any literature references which were contrary to the information provided or referenced by Allergan in this application for this indication.

4.4 Data Quality and Integrity

There is no evidence that the submitted study and previously submitted studies were not conducted in accordance with acceptable clinical ethical standards.

4.5 Compliance with Good Clinical Practices

All studies were conducted in accordance with accepted clinical and ethical standards.

4.6 Financial Disclosures

The applicant has adequately disclosed financial arrangements with clinical investigators as recommended in the FDA guidance for industry on Financial Disclosure by Clinical Investigators for 190342-024T. The forms for -012T, -013T, -019T, and -023T have previously been submitted to the NDA

5 CLINICAL PHARMACOLOGY

Not applicable to this amendment. There are no remaining issues. See previous clinical pharmacology reviews for this NDA.

The submitted label has been reviewed by Clinical Pharmacology and appropriate changes incorporated.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

The indication sought in this new drug application is:

> Combigan (brimonidine tartrate/ timolol ophthalmic solution) 0.2%/0.5% is indicated for the reduction of elevated intraocular pressure in patients with glaucoma or ocular hypertension who require adjunctive or replacement therapy due to inadequately controlled IOP.

6.1.1 Methods

All submitted clinical study reports, clinical protocols, summary documents, and cited references were reviewed. All submitted studies were reviewed separately and subsequently assessed in aggregate.

The application was submitted in electronic format including proposed draft labeling and Case Report Forms for discontinued subjects for the submitted trial 190342-024T.

The medical reviewer conducted a PubMed electronic literature search to supplement the submitted review of the relevant literature. There was no significant new information found in the published literature.

6.1.2 General Discussion of Endpoints

See previous clinical reviews for this New Drug Application.

The data contained in the original NDA, in an amendment dated September 13, 2004, and in an amendment dated June 29, 2006, did not adequately show that each component made a contribution to the claimed effect of the combination product.

An alternative dosing regimen could provide a useful product if it could be demonstrated that the safety profile of the proposed combination product is better than that of the individual agents taken as currently permitted in the approved labeling; the combination's IOP-lowering ability is inferior (approximately 1-2 mmHg) to that of brimonidine and timolol given concomitantly.

Study 190342-24T submitted in this May 2, 2007, amendment was designed to address this deficiency by evaluating and comparing the safety of fixed combination BID with 0.2% Alphagan TID and 0.5% timolol BID given concurrently following ocular administration for 10 days in glaucoma and ocular hypertension patients.

By finding a significant between-group difference in the current severity of Sleepiness Responders (a clinically relevant endpoint associated with decreased reaction time and impaired cognitive performance), Allergan has demonstrated that the fixed combination, alternative dosing regimen would provide a useful product because the safety profile of the proposed combination product is better than that of the individual agents taken as currently permitted in the approved labeling. The combination's IOP-lowering ability is, however, inferior (approximately 1-2 mmHg) to that of brimonidine and timolol given concomitantly.

NDA 21-398 for Combigan (brimonidine tartrate/timolol maleate ophthalmic solution) 0.2%/0.5% is recommended for approval with the labeling revisions found in the review; the IOP-lowering of Combigan BID was slightly less than that seen with the concomitant administration of 0.5% timolol BID and 0.2% brimonidine TID.

See Section 7.3 of this review for a more detailed regulatory history.

6.1.3 Study Design

Study Number: 190342-024T

Study Initiation Date: 25 November 2005
Study Completion Date: 26 January 2007

A Multi-Center, Randomized, Double-Masked, Parallel-Group Study to Evaluate the Safety of BID (Twice-Daily) Administration of 0.2% Brimonidine Tartrate/ 0.5% Timolol Fixed Combination Ophthalmic Solution Compared with Alphagan (0.2% Brimonidine Tartrate) TID (Three Times Daily) and 0.5% Timolol BID Given Concurrently in Glaucoma or Ocular Hypertension Patients for Ten Days

Principal Investigator Name (Number), Address	Other Participants Name, Degree (Role)	N	Patient Numbers
Jason Bacharach, MD (3761) North Bay Eye Associates, Inc 104 Lynch Creek Way Suites 15 & 12 Petaluma California 94954 USA	[redacted]	4	80201-80250
Luca Brigatti, MD (4084) University of Arizona Department of Ophthalmology Clinical Studies 707 North Alvernon Way Suite 301, 3rd Floor Tucson Arizona 85711 USA	[redacted]	5	81101-81150

Principal Investigator Name (Number), Address	Other Participants Name, Degree (Role)	N	Patient Numbers
Louis B Cantor, MD (2117) University Hospital and Outpatient Center 550 North University Boulevard Indianapolis Indiana 46202 USA	[redacted]	24	81001-81050
E Randy Craven, MD (2027) 8101 East Lowry Blvd. Suite #110 Denver, Colorado 80230 USA	[redacted]	9	80301-80350
William F Davitt, III, MD (3809) Corona Research Consultants, Inc 8815 Dyer Street, Suites 130 and 165 El Paso, Texas 79904 USA	None	20	80351-80400
Douglas G. Day, MD (2851) Omni Eye Services 5505 Peachtree-Dunwoody Road, Suite 300 Atlanta Georgia 30339 USA	None	36	80901-80950 81701-81750
Harvey B. DuBiner, MD (2450) Eye Care Centers Management, Inc. Clayton Eye Center 1000 Corporate Center Drive, Suite 100 and 120 Morrow, Georgia 30260 USA	None	25	80251-80300
Robert M Feldman, MD (2910) Hermann Eye Center 6411 Fannin Street, 7th Floor Jones Houston, Texas 77030 USA	[redacted]	10	81051-81100
John Foley, MD (3768) Eastern Shore Eye Center 3297 Broad Street Exmore, Virginia 23350 USA	None	15	81151-81200
Michael S Korenfeld, MD (4666) Comprehensive Eye Care, Ltd 901 East Third Street Washington, Missouri 63090 USA	[redacted]	54	80801-80850 81551-81600

Principal Investigator Name (Number), Address	Other Participants Name, Degree (Role)	N	Patient Numbers
Theodore Krupin, MD (2871) University Eye Specialists 676 North Saint Clair Suite 320 Chicago, Illinois 60611 USA	None	1	80401-80450
Donald McCormack, MD (1942) Boulder Medical Center PC 2750 Broadway Boulder, Colorado 80304 USA	[redacted]	8	81201-81250
Thomas K Mundorf, MD (1485) Presbyterian Medical Tower Laboratory 1718 E. Fourth Street, Suite 102 Charlotte, North Carolina 28204 USA	None	25	80451-80500
Michael Rotberg, MD (2037) Charlotte Eye, Ear, Nose, and Throat Associates, PA 6035 Fairview Road Charlotte, North Carolina 28210 USA	[redacted]	21	80951-81000
Kenneth Sall, MD (2707) Sall Eye Research Medical Center 11423 187th Street, Suite 200 Artesia, California 90701 USA	None	100	80101-80200 81451-81550
Howard I Schenker, MD (2429) Rochester Ophthalmological Group PC 2100 South Clinton Avenue Rochester, New York 14618 USA	[redacted]	85	81251-81300 81651-81700
Steven T Simmons, MD (1655) Glaucoma Consultants of the Capital Region 1240 New Scotland Road, Suite 201 Slingerlands, New York 12159 USA	[redacted]	2	81351-81400
Michael Tepedino, MD (3212) Cornerstone Eye Care 307 Lindsay Street High Point, North Carolina 27262 USA	None	49	81301-81350 81601-81650

Principal Investigator Name (Number), Address	Other Participants Name, Degree (Role)	N	Patient Numbers
Gail Torkildsen, MD (4615) Ophthalmic Research Associates 863 Turnpike Street North Andover, Massachusetts 01845 USA	[redacted]	9	80701-80750
Jacob T Wilensky, MD (0296) University of Illinois at Chicago 1855 West Taylor, Room 2.05 Chicago, Illinois 60612 USA	[redacted]	4	80551-80600
Robert Williams, MD (2710) Taustine Eye Center 1169 Eastern Parkway, Suite 3427 Louisville, Kentucky 40217 USA	None	17	80601-80650
David Wirta, MD (3276) David Wirta, Inc Eye Research Foundation 1501 Superior Avenue, Suite 303 Newport Beach, California 92663 USA	None	81	80001-80100 81751-81800

This study was a multicenter, randomized, double-masked, parallel-group safety study consisting of 5 scheduled visits: Screening (Day -50 to Day -3), Baseline (Day -1), Day 1, Day 9, and Day 10. Patients with OHT, chronic open-angle glaucoma, chronic angle-closure glaucoma with a patent iridotomy/iridectomy, pseudoexfoliative glaucoma, or pigmentary glaucoma who required bilateral treatment were eligible to enter the study.

A total of 604 patients were enrolled (598 planned) and assigned in a 1:1 allocation to 1 of 2 masked treatment groups:

- Combination: 0.2% brimonidine tartrate/0.5% timolol combination ophthalmic solution administered BID (morning and evening), or
- Concurrent: Alphagan ophthalmic solution (0.2% brimonidine tartrate) administered TID (morning, afternoon, and evening) and timolol ophthalmic solution (0.5% timolol) administered BID (morning and evening).

For patients in the Combination group, the Combination was administered BID (morning and evening) with brimonidine vehicle administered TID (morning, afternoon, and evening) to maintain proper masking.

Patients began study medication dosing in the morning between 07:00 and 09:00 (Hour 0) of Day 1 and dosing continued through Hour 6 on Day 10. On Days 1, 9 and 10, dosing was performed by the site personnel at Hours 0 and 6. Patients administered the Hour 12 dose on Days 1 and 9 and all doses on Days 2 to 8.

No efficacy measurements were performed for this study. This study directly compared the safety of Combination and Concurrent by specifically assessing sleepiness, dry mouth, and dizziness as follows:

- the current severity of sleepiness (using the 7-point Stanford Sleepiness Scale [SSS] questionnaire with 1 being the most alert and 7 being the most tired); dry mouth (using a 5-point scale questionnaire with 1 being "not experiencing the symptom at all" and 5 being "intolerable"); and dizziness (using a 5-point scale questionnaire with 1 being "not experiencing the symptom at all" and 5 being "intolerable");
- an assessment of the amount of saliva based on the weight of an unstimulated saliva collection;
- the frequency of dry mouth, sleepiness, and dizziness since the patient's last visit as assessed by a retrospective 5-point scale questionnaire with 1 being "never" and 5 being "always."

The primary safety assessment endpoint was the proportion of "Sleepiness Responders" defined as a patient who at any time over the course of the study (i.e., on Day 1, Day 9, or Day 10) had a current severity of sleepiness score of at least 4 (somewhat foggy, let down) as well as at least a 2-unit increase from the baseline score.

Standard safety measures performed during the study included adverse events (AEs), blood pressure (BP), and pulse rate (PR), IOP, visual acuity (VA), and biomicroscopy.

Inclusion Criteria

The following criteria were requirements for entry into the study:

1) Male or Female, at least 18 years of age and legal age of consent
2) Written informed consent and authorization obtained prior to any study related procedures
3) Patient had ocular hypertension, chronic open-angle glaucoma, chronic angle-closure glaucoma with patent iridotomy/iridectomy, pseudoexfoliative glaucoma, or pigmentary glaucoma in both eyes
4) A best-corrected visual acuity (BCVA) score equivalent to a Snellen acuity of 20/100 or better in each eye, using a logarithmic visual acuity chart for testing at 10 feet
5) Patient had a stable IOP and was able to be washed out of his/her IOP-lowering medications (if applicable)
6) At Baseline, the patient was appropriately washed out of all IOP-lowering medications

7) Patient required bilateral IOP-lowering treatment
8) Acceptable fasting blood analysis (hematology, blood chemistry) and urinalysis results (acceptable blood and urinalysis results were those within the reference range as defined by the laboratory or results "out-of-range" but still acceptable to the investigator and consistent with the study inclusion / exclusion criteria)
9) Negative screen for drugs of abuse, nicotine, and alcohol
10) A negative urine pregnancy test for female patients of childbearing potential at the baseline visit. A female was considered to be of childbearing potential unless she was post-menopausal or without a uterus and/or both ovaries.
11) Ability to follow study instructions and likely to complete all required visits.

Exclusion Criteria

The following were criteria for exclusion from participating in the study:

1) Any uncontrolled systemic disease
2) Patients with any abnormality of the lids, ocular surface, or lacrimal duct system that could have affected absorption
3) Active ocular disease (e.g., uveitis, ocular infections, chronic blepharitis, or severe dry eye), that in the opinion of the investigator would have interfered with the interpretation of the study data. Myopia, strabismus, and cataracts were allowed provided other criteria were met.
4) History of excessive consumption of alcohol, or alcohol-dependency within the last 2 years. Use of alcohol within 3 days prior to baseline, or anticipated use during the study
5) History of illicit drug abuse (e.g., phencyclidine, benzodiazepines, cannabinoids, amphetamines, barbiturates, cocaine, and opiates)
6) History of excessive consumption of xanthine-containing products, or caffeine dependency, or anticipated excessive use during the course of the study
7) Required use of ocular medications (post-baseline visit) other than the study medication (occasional use of artificial tears was allowed)
8) Treatment with any alpha-agonists, alpha-antagonists (including medications for benign prostate hyperplasia), anticholinergic, antihistamines, or cold medications within 2 weeks prior to baseline or during the study
9) Patients who anticipated using tobacco products during the study
10) Patients who anticipated drinking more than 24 ounces of caffeinated drinks per day during the study
11) Females who were pregnant, nursing, or planning a pregnancy or who were of childbearing potential and not using a reliable method of contraception
12) Contraindication to beta-adrenoreceptor antagonist therapy. Contraindications included, but were not limited to, chronic obstructive pulmonary disease, bronchial asthma, sinus bradycardia, second and third degree atrioventricular block, uncontrolled congestive heart failure, history of severe myocardial infarction, or clinically relevant low or high heart (pulse) rate or blood pressure.
13) Patients with cardiovascular disease were not enrolled unless their disease was controlled and clearance had been obtained from the treating primary care physician or cardiologist
14) Contraindication to brimonidine therapy such as concurrent use of monoamine oxidase (MAO) inhibitor therapy

15) Concurrent use or anticipated treatment with adrenergic augmenting psychotropic drugs (i.e., tricyclic antidepressants such as desipramine or amitriptyline)
16) Patient had a sleep disorder or patient could not or was unwilling to sleep approximately 8 hours/night for the week before and during the study
17) Anticipated wearing of contact lenses during the study (use of soft lenses should have been discontinued at least 2 days prior to baseline, and use of rigid gas permeable [RGP] or hard contact lenses should have been discontinued at least 1 week prior to baseline)
18) Current enrollment in an investigational drug or device study or participation in such a study within 30 days prior to the baseline visit
19) Patient had a condition or was in a situation which, in the investigator's opinion, may have put the patient at significant risk, may have confounded the study results, or may have interfered significantly with the patient's participation in the study.

Schedule of Visits and Measurements 190342-024T

Visits and Timepoints	Consent[a] / Hx / PE	Lab Draw[b]	Eye Exam[c]	Preg Test[d]	BP / PR	SME[e] / AE	Question -naires[f]	Saliva Assess[g]	Dosing
Screening Day -50 to -3									
Anytime	X	X	X[c]		X	X			
Baseline, Day -1									
15:00-17:00			X	X	X	X	X	X	
Day 1									
Hour 0					X	X			X
Hour 6									X
Hour 8							X		
Day 9									
Hour 0					X	X			X
Hour 6									X
Hour 8							X		
Day 10									
Hour 0					X	X			X
Hour 6									X
Hour 8			X				X	X	
Early Exit									
Anytime			X		X	X	X	X	

Abbreviations: Hx = History, Lab = Laboratory, Preg = Pregnancy, BP = Blood Pressure, PR = Pulse Rate, AE = Adverse Event, SME = Serious Medical Event, Assess = Assessment, PE = Physical Exam

a Consent included study Informed Consent and Authorization; medical and social histories were taken.

b Laboratory draw included fasting blood draw, urinalysis, and urine drug screen. Fasting should not have begun until after consent had been signed. Samples should have been collected and reviewed prior to randomization.

c Eye exam included visual acuity, biomicroscopy, and intraocular pressure. At the screening visit an ophthalmoscopy exam should have included cup/disc ratio.

d Pregnancy test for females of childbearing potential.

e SMEs were assessed between the time informed consent was signed and randomization into the study.

f Symptom questionnaires included dry mouth, dizziness, and sleepiness assessments.

g Patients should have had no food or drink at least 1 hour prior to assessment.

Source: Table 9.5-2

Demographics – ITT population

Variable	Combination N = 304	Concurrent N = 300	Total N = 604
Age (years)			
mean (range)	64.2 (21 to 94)	63.8 (24 to 94)	64.0 (21 to 94)
< 40	12 (3.9%)	9 (3.0%)	21 (3.5%)
40 - < 65	135 (44.4%)	132 (44.0%)	267 (44.2%)
≥ 65	157 (51.6%)	159 (53.0%)	316 (52.3%)
Sex			
male	120 (39.5%)	122 (40.7%)	242 (40.1%)
female	184 (60.5%)	178 (59.3%)	362 (59.9%)
Race			
black	57 (18.8%)	55 (18.3%)	112 (18.5%)
non-black			
Caucasian	193 (63.5%)	184 (61.3%)	377 (62.4%)
Asian	6 (2.0%)	10 (3.3%)	16 (2.6%)
Hispanic	45 (14.8%)	45 (15.0%)	90 (14.9%)
Other[a]	3 (1.0%)	6 (2.0%)	9 (1.5%)

Source: Table 14.1-2.1 and 14.1-2.2

a Other race included Indian, Euro-American, Pacific Islander/Hispanic, Persian, Pakistanian, Native American & Hispanic, American Indian - Native American.

Reviewer's Comments:

For the ITT/Safety population, demographics for the 2 treatment groups were comparable at baseline

6.1.4 Efficacy Findings

No efficacy measurements were performed during study 190342-024T.

Reviewer's Comments:

Only baseline intraocular pressure was measured in 190342-024T.

6.1.5 Clinical Microbiology

Not applicable to this application.

6.1.6 Efficacy Conclusions

No efficacy measurements were performed during study 190342-024T.

There is no new information submitted to alter the conclusion from the original NDA M.O. review:

- There are statistically significant differences in IOP at baseline between the combination and timolol in study 190342-012T.
- Neither study 190342-012T nor 190342-013T demonstrates a clinically significant contribution of brimonidine tartrate 0.2% to the combination product.
- There is a reproducible loss of IOP lowering ability of the combination versus brimonidine tartrate 0.2% seen in both phase 3 studies at hour 9 during each diurnal measurement.
- Neither study 190342-012T nor 190342-013T demonstrates a clinically significant contribution of timolol 0.5% to the combination product.

There is no new information submitted to alter the conclusion from the review of the September 13, 2004, M.O. review:

- Study 190342-019T fails to demonstrate that the efficacy of the combination product is equivalent to the efficacy attained when each of the individual components are dosed concurrently.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

All submitted clinical study reports, clinical protocols, summary documents, and cited references were reviewed. All submitted studies were reviewed separately and subsequently assessed in aggregate.

The application was submitted in electronic format including proposed draft labeling and Case Report Forms for discontinued subjects for the submitted trial 190342-024T.

The medical reviewer conducted a PubMed electronic literature search to supplement the submitted review of the relevant literature. There was no significant new information found in the published literature.

7.1.1 Deaths

No deaths were reported during study 190342-024T.

7.1.2 Other Serious Adverse Events

Table 7.1.2 - All Serious Adverse Events 190342-024T

Patient	Tx Group	Age/Sex/Race	Coded AE Term	Outcome	DC Due to AE
3768-81158	Combination	68/F/B	Cerebral infarction	Resolved w/Tx	Yes
4666-80833	Concurrent	85/F/C	Gastric ulcer hemorrhage	Resolved w/Tx	Yes
			Bradycardia	Resolved w/Tx	

Source: Table 14.3.2-1

Patient 3768-81158 (Combination)

This 68-year-old woman was randomized to the 0.2% brimonidine tartrate/0.5% timolol BID fixed combination ophthalmic solution for approximately one week when, on [redacted] she was hospitalized due to a **cerebral infarction**. The final hospital discharge summary characterized this event as an embolic stroke in a subject found to have atrial fibrillation on electrocardiogram and a mural thrombus in the left ventricle on ultrasound. It should also be noted that the subject was on a beta-blocker (metoprolol) at the time of the AE. The event resolved without sequelae.

The study drug was discontinued and the subject exited the study on 07/APR/06.

Patient 4666-80833 (Concurrent)

This 85-year-old woman was randomized to Alphagan TID and 0.5 % timolol BID (concurrent treatment) for approximately 2 days when she was hospitalized due to a **gastrointestinal bleeding ulcer**. She underwent an upper gastrointestinal series [redacted] and a colonoscopy [redacted]. During her hospitalization, on [redacted] **bradycardia** was also diagnosed and she underwent placement of a pacemaker [redacted]. At the time of this event, the subject's concomitant medication included a nonsteroidal anti-inflammatory drug (Aleve). The subject

had a past medical history of arrhythmia and was discharged with the diagnoses of mitral stenosis, atrial fibrillation, and sick sinus syndrome. Each event resolved without sequelae.

The study drug was discontinued and the subject exited the study on 30/JUN/06.

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

Table 7.1.3.1 – Discontinued Patients with Exit Reasons 190342-024T

Patient	Age/Sex/Race	Date of Exit	Date of 1st Dose	Reason for DC	Discontinuing AE	Safety	mITT
Combination							
2037-80954	64/M/C	06FEB06	31JAN06	AE	Allergic contact dermatitis	Yes	Yes
2450-80276	75/F/C	08MAR06	28FEB06	Other: noncompliant w/ dosing		Yes	No
2707-81469	68/M/H	22SEP06	13SEP06	Other: lost study meds		Yes	Yes
3276-80093	67/M/A	12DEC06	06DEC06	Personal (job scheduling problem)		Yes	Yes
3768-81158	68/F/B	07APR06	30MAR06	AE	Cerebral infarction	Yes	Yes
Concurrent							
1942-81201	75/M/C	20MAR06	14MAR06	AE	Allergic conjunctivitis Lid dermatitis	Yes	Yes
2429-81655	62/M/C	08JAN07	03JAN07	AE	Allergic conjunctivitis	Yes	Yes
2450-80266	50/B/F	28MAR06	28FEB06	Personal (elective hysterectomy)		Yes	Yes
3212-81604	79/F/C	02NOV06	24OCT06	Personal (unspecified "emergency")		Yes	Yes
3276-80018	81/F/A	05APR06	28MAR06	AE	Alphagan allergy	Yes	Yes
3276-80067	58/F/H	26SEP06	26SEP06	Personal (sick mother)		Yes	No
4666-80807	27/M/C	22MAR06	22MAR06	Lost to follow-up		Yes	No
4666-80833	85/F/C	30JUN06	21JUN06	AE	Bradycardia	Yes	Yes
4666-80836	47/M/C	09JUN06	07JUN06	AE	Iritis	Yes	Yes

Source: Table16.2.1-1 and CRFs

Reviewer's Comments:

It is unclear how subject 3276-80018 (concurrent therapy arm) was determined to have an allergy to Alphagan alone based on review of the submitted CRFs.

7.1.3.2 Adverse events associated with dropouts

See Table 7.1.3.1. The most frequent adverse event leading to discontinuation in 190342-024T for both treatment groups was allergic conjunctivitis.

7.1.5 Common Adverse Events

Table 7.1.5 - Number (%) of Patients with Adverse Events Regardless of Causality Reported by at Least 1% of Patients in Either Treatment Group (Safety Population) 190342-024T

SYSTEM ORGAN CLASS Preferred Term[a]	Combination N = 304	Concurrent N = 300	P-Value[b]
EYE DISORDERS			
eye irritation	10 (3.3%)	4 (1.3%)	0.110
eye pain	9 (3.0%)	2 (0.7%)	0.035
conjunctival disorder	2 (0.7%)	3 (1.0%)	0.684
conjunctivitis allergic	1 (0.3%)	4 (1.3%)	0.214
foreign body sensation in eyes	1 (0.3%	3 (1.0%)	0.370
dry eye	0 (0.0%)	5 (1.7%)	0.030
eye pruritus	0 (0.0%)	3 (1.0%)	0.122
punctate keratitis	0 (0.0%)	3 (1.0%)	0.122
GASTROINTESTINAL DISORDERS			
dry mouth	3 (1.0%)	13 (4.3%)	0.010
nausea	1 (0.3%)	4 (1.3%)	0.214
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
fatigue	6 (2.0%)	1 (0.3%)	0.123
NERVOUS SYSTEM DISORDERS			
somnolence	4 (1.3%)	3 (1.0%)	> 0.999
headache	3 (1.0%)	4 (1.3%)	0.723
INVESTIGATIONS			
blood pressure increased	1 (0.3%)	3 (1.0%)	0.370

Source: Table 14.3-11.1

a System organ class and preferred terms from the MedDRA nomenclature, version 9.1

b P-value based on Pearson's chi-square or Fisher's exact test

The incidence of dry mouth was significantly higher with Concurrent (4.3%) than with Combination (1.0%).

For pooled common adverse event data tables, refer to the Medical Officer's review dated March 4, 2005, of the September 13, 2004, amendment. See Section 3.1.5.4, page 22.

7.1.5.6 Additional analyses and explorations

190342-024T Primary Endpoint

Current Severity of Sleepiness
Proportion of Sleepiness Responders
(Intent-to-Treat Population)

Combination (N=304)	Concurrent (N=300)	RR [a] (95% CI) [b]	P-value [c] Difference [d] (95% CI) [e]
28/304 (9.2%)	58/300 (19.3%)	2.10 (1.38, 3.20)	<0.001 -10.1% (-15.6%, -4.6%)

Note: A Sleepiness Responder is a patient who on Day 1, Day 9, or Day 10 has a SSS severity score of at least 4 as well as at least a 2-unit increase from the baseline score.
A patient missing the baseline assessment is deemed a responder if at least one-post baseline SSS score is >=4 and a non-responder otherwise. If all follow-up data are missing the patient is deemed a non-responder.
Severity Score: 1 = feeling active, vital, alert or wide awake, 2 = functioning at high levels, but not at peak; able to concentrate, 3 = awake, but relaxed; responsive but not fully alert, 4 = somewhat foggy, let down, 5 = foggy; losing interest in remaining awake; slowed down, 6 = sleepy, woozy, fighting sleep; prefer to lie down, 7 = no longer fighting sleep, sleep onset soon; having dream-like thoughts; asleep.
[a] Relative risk is the proportion of responders in the Concurrent group divided by the proportion of responders in the Combination group.
[b] Asymptotic 2-sided 95% confidence interval for the relative risk.
[c] P-value is from the general association statistic of the Cochran-Mantel-Haenszel (CMH) test, stratified by investigator.
[d] Difference of the proportions calculated as Combination group minus the Concurrent group.
[e] 2-sided 95% confidence interval of the difference in proportions calculated using the normal approximation to the binomial distribution.

Source: Table 14.3-2.1

The primary endpoint of 190342-024T was the proportion of current severity of Sleepiness Responders in the ITT population (over the course of the study) using the Stanford Sleepiness Scale (SSS).

There was a highly statistically significant difference between the treatment groups favoring Combination for the primary safety variable with 9.2% (28/304) responders in the Combination group and 19.3% (58/300) responders in the Cprimary endpit, oncurrent group, $p < 0.001$. The relative risk (RR) was 2.10, with a 95% confidence interval (CI) of 1.38 to 3.20).

Reviewer's Comments:

An alternative dosing regimen could provide a useful product if it could be demonstrated that the safety profile of the proposed combination product is better than that of the individual agents taken as currently permitted in the approved labeling; the combination's IOP-lowering ability is inferior (approximately 1-2 mmHg) to that of brimonidine and timolol given concomitantly.

This particular endpoint, the proportion of current severity of Sleepiness Responders in the ITT population (over the course of the study) using the Stanford Sleepiness Scale (SSS), is sufficient to offset the combination's inferior IOP-lowering ability and support approval. Inappropriate sleepiness is associated with decreased reaction time and impaired cognitive performance.

190342-024T Supplemental Analysis - mITT

Current Severity of Sleepiness
Proportion of Sleepiness Responders
(Modified Intent-to-Treat Population)

Combination (N=290)	Concurrent (N=287)	RR [a] (95% CI) [b]	P-value [c] Difference [d] (95% CI) [e]
28/290 (9.7%)	55/287 (19.2%)	1.98 (1.30, 3.04)	0.001 -9.5% (-15.2%, -3.8%)

Note: A Sleepiness Responder is a patient who on Day 1, Day 9, or Day 10 has a SSS severity score of at least 4 as well as at least a 2-unit increase from the baseline score.
Severity Score: 1 = feeling active, vital, alert or wide awake, 2 = functioning at high levels, but not at peak; able to concentrate, 3 = awake, but relaxed; responsive but not fully alert, 4 = somewhat foggy, let down, 5 = foggy; losing interest in remaining awake; slowed down, 6 = sleepy, woozy, fighting sleep; prefer to lie down, 7 = no longer fighting sleep, sleep onset soon; having dream-like thoughts; asleep.
The mITT population consists of the subset of the safety population who are >= 40 years of age, and who had a baseline evaluation and at least one post-baseline evaluation for the primary assessment (SSS).
[a] Relative risk is the proportion of responders in the Concurrent group divided by the proportion of responders in the Combination group.
[b] Asymptotic 2-sided 95% confidence interval for the relative risk.
[c] P-value is from the general association statistic of the Cochran-Mantel-Haenszel (CMH) test, stratified by investigator.
[d] Difference of the proportions calculated as Combination group minus the Concurrent group.
[e] 2-sided 95% confidence interval of the difference in proportions calculated using the normal approximation to the binomial distribution.

Source: Table 14.6-10

In the mITT population[2], there was a highly statistically significant difference between the treatment groups for the primary safety variable with 9.7% (28/290) Sleepiness Responders in the Combination group compared to 19.2% (55/287) in the Concurrent group, p = 0.001. The RR was 1.98, with a 95% CI of 1.30 to 3.04.

Reviewer's Comments:

The mITT population provides support for the primary endpoint, i.e. the proportion of current severity of Sleepiness Responders in the ITT population (over the course of the study) using the Stanford Sleepiness Scale (SSS). Inappropriate sleepiness is associated with decreased reaction time and impaired cognitive performance.

[2] The mITT population included a subset of 577 patients (290 in the Combination group and 287 in the Current group) from the safety population who were ≥ 40 years of age and who had a baseline evaluation and at least 1 post-baseline evaluation for the primary safety assessment.

190342-024T Secondary Endpoints

Current Severity of Dry Mouth
Proportion of Dry Mouth Responders
(Intent-to-Treat Population)

Combination (N=304)	Concurrent (N=300)	RR [a] (95% CI) [b]	P-value [c] Difference [d] (95% CI) [e]
45/304 (14.8%)	72/300 (24.0%)	1.62 (1.16, 2.27)	0.005 -9.2% (-15.5%, -2.9%)

Note: A Dry Mouth Responder is a patient who on Day 1, Day 9, or Day 10 has a Current Severity of Dry Mouth score of at least 3 as well as at least a 1-unit increase from the baseline score.
A patient missing the baseline assessment is deemed a responder if at least one post-baseline dry mouth score is >=3 and a non-responder otherwise. If all follow-up data are missing the patient is deemed a non-responder.
Severity Score: 1 = not experiencing the symptom at all, 2 = mild, 3 = moderate, 4 = severe, 5 = intolerable.
[a] Relative risk is the proportion of responders in the Concurrent group divided by the proportion of responders in the Combination group.
[b] Asymptotic 2-sided 95% confidence interval for the relative risk.
[c] P-value is from the general association statistic of the Cochran-Mantel-Haenszel (CMH) test, stratified by investigator.
[d] Difference of the proportions calculated as Combination group minus the Concurrent group.
[e] 2-sided 95% confidence interval of the difference in proportions calculated using the normal approximation to the binomial distribution.

Source: Table 14.3-3.1

There was a statistically significant difference between the treatment groups favoring Combination with 14.8% (45/304) responders in the Combination group and 24.0% (72/300) responders in the Concurrent group, p = 0.005. The RR (95% CI) was 1.62 (1.16 to 2.27).

Reviewer's Comments:

Although not as clinically relevant an endpoint as current severity of sleepiness, current severity of dry mouth demonstrates a statistically significant between-group difference.

Current Severity of Sleepiness in Patients < 65 Years Old
Proportion of Sleepiness Responders
(Intent-to-Treat Population)

Combination (N=147)	Concurrent (N=141)	RR [a] (95% CI) [b]	P-value [c] Difference [d] (95% CI) [e]
17/147 (11.6%)	29/141 (20.6%)	1.78 (1.02, 3.09)	0.037 -9.0% (-17.4%, -0.6%)

Note: A Sleepiness Responder is a patient who on Day 1, Day 9, or Day 10 has a SSS severity score of at least 4 as well as at least a 2-unit increase from the baseline score.
A patient missing the baseline assessment is deemed a responder if at least one-post baseline SSS score is >=4. If all follow-up data are missing the patient is deemed a non-responder.
Severity Score: 1 = feeling active, vital, alert or wide awake, 2 = functioning at high levels, but not at peak; able to concentrate, 3 = awake, but relaxed; responsive but not fully alert, 4 = somewhat foggy, let down, 5 = foggy; losing interest in remaining awake; slowed down, 6 = sleepy, woozy, fighting sleep; prefer to lie down, 7 = no longer fighting sleep, sleep onset soon; having dream-like thoughts; asleep.
[a] Relative risk is the proportion of responders in the Combination group divided by the proportion of responders in the Concurrent group.
[b] Asymptotic 2-sided 95% confidence interval for the relative risk.
[c] A Pearson's chi-square test is performed to evaluate the equality of proportions between treatment groups. If 25% or more of the cells have expected counts less than 5, then Fisher's exact test is used instead.
[d] Difference of the proportions calculated as Combination group minus the Concurrent group.
[e] 2-sided 95% confidence interval of the difference in proportions calculated using the normal approximation to the binomial distribution.

Source: Table 14.3-4.1

There was a statistically significant difference between the treatment groups favoring Combination with 11.6% (17/147) responders in the Combination group and 20.6% (29/141) responders in the Concurrent group, p = 0.037 . The RR (95% CI) was 1.78 (1.02 to 3.09).

Reviewer's Comments:

Although not as clinically relevant an endpoint as current severity of sleepiness, current severity of sleepiness in subjects < 65 years old demonstrates a statistically significant between-group difference.

Inappropriate Sleepiness
Proportion of Responders
(Intent-to-Treat Population)

Combination (N=304)	Concurrent (N=300)	RR [a] (95% CI) [b]	P-value [c] Difference [d] (95% CI) [e]
77/304 (25.3%)	89/300 (29.7%)	1.17 (0.90, 1.52)	0.239 -4.3% (-11.5%, 2.8%)

Note: Inappropriate sleepiness is derived from Retrospective Symptom Questionnaire Question 6: Have You Felt Sleepy When You Feel You Shouldn't? A Responder is a patient who on Day 1, Day 9, or Day 10 has a score of at least 3 as well as at least a 1-unit increase from the baseline score.
A patient missing the baseline assessment is deemed a responder if at least one post-baseline score is >=3 and a non-responder otherwise. If all follow-up data are missing the patient is deemed a non-responder.
Frequency Score: 1 = Never, 2 = Rarely, 3 = Sometimes, 4 = Mostly, 5 = Always
[a] Relative risk is the proportion of responders in the Concurrent group divided by the proportion of responders in the Combination group.
[b] Asymptotic 2-sided 95% confidence interval for the relative risk.
[c] P-value is from the general association statistic of the Cochran-Mantel-Haenszel (CMH) test, stratified by investigator.
[d] Difference of the proportions calculated as Combination group minus the Concurrent group.
[e] 2-sided 95% confidence interval of the difference in proportions calculated using the normal approximation to the binomial distribution.

Source: Table 14.3-5.1

The proportion of Inappropriate Sleepiness Responders was 25.3% (77/304) in the Combination group and 29.7% (89/300) in the Concurrent group, p = 0.239. The RR (95% CI) was 1.17 (0.90 to 1.52). This difference was not statistically significant.

Reviewer's Comments:

Although not as clinically relevant an endpoint as current severity of sleepiness, inappropriate sleepiness demonstrates a statistically significant between-group difference.

190342-024T Additional Analyses of Sleepiness by Age, Sex and Race

Subgroup	Combination N = 304	Concurrent N = 300	RR[a]	P-Value[b]
< 65 years	11.6% (17/147)	20.6% (29/141)	1.78	0.037
≥ 65 years	7.0% (11/157)	18.2% (29/159)	2.60	0.003
male	6.7% (8/120)	14.8% (18/122)	2.21	0.042
female	10.9% (20/184)	22.5% (40/178)	2.07	0.003
black	5.3% (3/57)	20.0% (11/55)	3.80	0.018
non-black	10.1% (25/247)	19.2% (47/245)	1.90	0.004

Source: Tables 14.3-4.1, 14.6-7.2 to 14.6-7.6

a Relative risk (RR) is the proportion of responders in the Concurrent group divided by the proportion of responders in the Combination group

b P-value from Pearson's chi-square test or Fisher's exact text

The proportion of Sleepiness Responders was less with Combination than Concurrent in each demographic subgroup

7.1.6 Less Common Adverse Events

For 190342-024T, see Section 7.1.5 Common Adverse Events in this review.

Reviewer's Comments:

For pooled common adverse event data tables for the Phase 3 trials, refer to the Medical Officer's review dated March 4, 2005, of the September 13, 2004, amendment. See Section 3.1.5.4, page 22.

7.1.7 Laboratory Findings

Clinical laboratory data were collected at Screening only in 190342-024T. According to the protocol, no post-baseline laboratory data were collected.

7.1.8 Vital Signs

There were no clinically meaningful within or between-group differences in the change from baseline for systolic blood pressure, diastolic blood pressure, or mean pulse rate at any follow-up visit.

Vital Signs Assessment: Baseline and Change from Baseline
Systolic Blood Pressure (mm Hg)
(Safety Population)

		Combination (N=304)	Concurrent (N=300)	P-value[a]
Day 1				
	N	304	300	0.228
	Mean	131.2	132.7	
	SD	14.75	15.90	
	Median	130.0	132.0	
	Min	90	92	
	Max	178	209	
Day 9				
	N	298	291	0.093
	Mean	0.1	1.9	
	SD	13.34	12.40	
	Median	0.0	1.0	
	Min	-45	-32	
	Max	45	45	
	P-value[b]	0.900	0.010	
Day 10				
	N	301	297	0.106
	Mean	-1.2	0.6	
	SD	13.69	13.04	
	Median	-2.0	1.0	
	Min	-47	-46	
	Max	46	40	
	P-value[b]	0.124	0.463	

Note: Day 1 measurements are considered as baseline measurements.
[a] A 1-way ANOVA is performed to evaluate the difference between treatment groups.
[b] P-value for within-group comparison is based on paired t-test.

Source: Table 14.3-18

Vital Signs Assessment: Baseline and Change from Baseline
Diastolic Blood Pressure (mm Hg)
(Safety Population)

		Combination (N=304)	Concurrent (N=300)	P-value[a]
Day 1				
	N	304	300	0.432
	Mean	74.2	74.8	
	SD	8.86	9.74	
	Median	74.0	75.5	
	Min	48	38	
	Max	102	112	
Day 9				
	N	298	291	0.016
	Mean	0.1	1.9	
	SD	8.26	9.12	
	Median	0.0	2.0	
	Min	-26	-20	
	Max	20	38	
	P-value[b]	0.769	<0.001	
Day 10				
	N	301	297	0.041
	Mean	-0.5	1.0	
	SD	8.56	9.78	
	Median	-1.0	0.0	
	Min	-25	-27	
	Max	22	42	
	P-value[b]	0.267	0.081	

Note: Day 1 measurements are considered as baseline measurements.
[a] A 1-way ANOVA is performed to evaluate the difference between treatment groups.
[b] P-value for within-group comparison is based on paired t-test.

Source: Table 14.3-19

Vital Signs Assessment: Baseline and Change from Baseline
Pulse Rate (bpm)
(Safety Population)

		Combination (N=304)	Concurrent (N=300)	P-value[a]
Day 1				
	N	304	300	0.218
	Mean	72.5	71.5	
	SD	9.75	9.32	
	Median	72.0	72.0	
	Min	48	48	
	Max	101	101	
Day 9				
	N	298	291	0.097
	Mean	-2.7	-1.7	
	SD	7.83	7.43	
	Median	-2.0	-2.0	
	Min	-35	-24	
	Max	24	20	
	P-value[b]	<0.001	<0.001	
Day 10				
	N	301	297	0.077
	Mean	-2.7	-1.5	
	SD	8.09	8.48	
	Median	-2.0	-2.0	
	Min	-22	-32	
	Max	23	32	
	P-value[b]	<0.001	0.002	

Note: Day 1 measurements are considered as baseline measurements.
[a] A 1-way ANOVA is performed to evaluate the difference between treatment groups.
[b] P-value for within-group comparison is based on paired t-test.

Source: Table 14.3-20

7.1.9 Electrocardiograms (ECGs)

No electrocardiograms were obtained in 190342-024T. The proposed labeling with Reviewer changes contains adequate warnings/contraindications regarding beta-adrenergic blockade.

7.1.10 Immunogenicity

Not applicable. Drug product is not expected to be immunogenic.

7.1.11 Human Carcinogenicity

Not applicable. Neither brimonidine tartrate nor timolol maleate had positive genotoxicity or animal carcinogenicity findings to warrant a systematic assessment of all human tumors reported during drug development.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

Not applicable. This is not a therapeutic class with known abuse potential or apparent withdrawal potential.

7.1.14 Human Reproduction and Pregnancy Data

There are no adequate and well-controlled studies in pregnant women; however, in animal studies, brimonidine crossed the placenta and entered into the fetal circulation to a limited extent. Because animal reproduction studies are not always predictive of human response, this drug product should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus.

Timolol has been detected in human milk following oral and ophthalmic drug administration. It is not known whether brimonidine tartrate is excreted in human milk, although in animal studies, brimonidine tartrate has been shown to be excreted in breast milk. Because of the potential for serious adverse reactions from this drug product in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

7.1.15 Assessment of Effect on Growth

See Section 8.4 Pediatrics. There has been no effect on growth noted for either brimonidine tartrate or timolol maleate.

7.1.16 Overdose Experience

No information is available on overdosage with this drug product in humans. There have been reports of inadvertent overdosage with timolol ophthalmic solution resulting in systemic effects similar to those seen with systemic beta-adrenergic blocking agents such as dizziness, headache, shortness of breath, bradycardia, bronchospasm, and cardiac arrest.

7.1.17 Postmarketing Experience

See Safety Update, Section 7.2.9.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

See Section 4.2 regarding clinical trial listings.

The global sales distribution data (outside the US) for 01-Dec-2005 to 30-Sep-2006 is found below:

Worldwide Bottle Distribution

Europe	Rest of World	*Total
[redacted]		

* Excludes US distribution as US application is pending approval.

Combigan is intended for chronic therapy. Since each bottle is designed to last approximately one month, the estimated exposure is 95,692 patient-years.

During the same period from 01-Dec-2005 to 30-Sep-2006, approximately 3,208 patients were exposed to brimonidine tartrate/timolol combination during Allergan-sponsored trials.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

7.2.2.1 Other studies

See Section 4.2 regarding clinical trial listings.

7.2.2.2 Postmarketing experience

See Safety Update, Section 7.2.9.

7.2.2.3 Literature

A literature search conducted by this reviewer failed to identify any literature references which were contrary to the information provided or referenced by Allergan in this application for this indication.

7.2.3 Adequacy of Overall Clinical Experience

An adequate number of subjects were exposed to the drug product, including adequate demographic subsets. The doses and durations of exposure were adequate to assess safety for the intended use.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

Not applicable. There was no special animal or in vitro testing performed, See the previous Pharmacology/Toxicology reviews for more detail.

7.2.5 Adequacy of Routine Clinical Testing

The routine clinical testing of this drug product utilized adequate hematological, blood chemistry, and urinalysis evaluations for its component drug classes.

The methods and tests used and their frequency was adequate to effectively monitor the patient population.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

The metabolic, clearance, and interaction workup was adequate.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

The applicant's evaluation of potential adverse events for this pharmacological class of drug is adequate.

7.2.8 Assessment of Quality and Completeness of Data

The DSI Clinical Inspection Summary for -024T is pending. Previously inspected sites are reliable and be considered acceptable for approval of this NDA.

7.2.9 Additional Submissions, Including Safety Update

This is the third Periodic Safety Update Report (PSUR) for Combigan (brimonidine tartrate/timolol maleate ophthalmic solution) 0.2%/0.5%. It summarizes safety information received by Global Regulatory Affairs at Allergan from worldwide sources between 09 December 2005 and 10 October 2006. Combigan was first approved in Canada on 9 December 2003 and was approved in 33 countries for the treatment of glaucoma or ocular hypertension as of October 10, 2006. This PSUR does not cover products containing brimonidine or timolol alone.

In the ten months covered by this PSUR approximately [redacted] were distributed. Approximately 3,208 additional people were exposed to Combigan in Allergan-sponsored trials during this period.

Overall, the adverse events reported during this period reveal no significant changes in the type of events received for Combigan. For pooled common adverse event data tables, refer to the Medical Officer's review dated March 4, 2005, of the September 13, 2004, amendment. See Section 3.1.5.4, page 22.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

BACKGROUND

Post-hoc analysis of the pooled phase 3 studies 012T/013T, patients receiving combination BID had a significantly lower incidence of somnolence than patients receiving brimonidine TID as shown in the following table:

Table 7.3 - Incidence of Somnolence in Studies 012T, 013T, and Pooled

Study	Combination	Brimonidine	Timolol	Combination vs Brimonidine P-value[a]	Combination vs Timolol P-value[a]
Study 012T	2.1% (4/192)	4.3% (8/186)	1.0% (2/195)	0.219	0.446
Study 013T	1.0% (2/193)	3.6% (7/196)	0.0% (0/197)	0.175	0.244
Pooled	1.6% (6/385)	3.9% (15/382)	0.5% (2/392)	0.044	0.174

Source: 12-month reports 190342-012T and 190342-013T, Section 14.3, Table 23.1; Summary of Clinical Safety, Section 2.7.4.7.2-1, Table 5.1

a P-value based on Pearson's chi-square test or Fisher's exact test as appropriate

The Agency did not accept these post-hoc analyses, but they did serve to generate the hypothesis that the safety profile of the proposed combination product is better than that of the individual agents taken as currently permitted in the approved labeling for somnolence. Sleepiness is associated with decreased reaction time and impaired cognitive performance, and the effect on vehicular crashes resulting in injury and death is well established. A study conducted by Connor et al (2002)[3] showed that an SSS score in the 4 to 7 range confers an 8-fold increased risk of a serious car crash over scores in the 1 to 3 range (odds ratio = 8.2).

Study 190342-023T was designed to address this hypothesis by evaluating and comparing the safety of fixed combination BID with 0.2% Alphagan TID and 0.5% timolol BID given concurrently) following ocular administration for 10 days in healthy, adult subjects.

Although Study 190342-023T demonstrated that the safety profile of the proposed combination product was numerically superior to the individual agents taken as currently permitted in their approved labeling in the incidence of oral dryness adverse events, this difference in adverse events was not sufficient to offset the combination's inferior IOP-lowering ability (approximately 1-2 mmHg) compared to that of brimonidine and timolol given concomitantly. It would have greatly boosted Allergan's claim that the safety profile of the proposed combination product is significantly better than that of the individual agents taken as currently permitted in their approved labeling had the proportion of sleepiness responders been demonstrated as statistically and clinically significant.

[3] Connor J, Norton R, Ameratunga S, et al. Driver sleepiness and risk of serious injury to car occupants: population based case control study. BMJ 2002;324:11-25.

After review of the statistical analysis plan for study 023T, the Agency suggested that Allergan consider examining the effect of age on these adverse events. In response, Allergan reanalyzed the adverse event of sleepiness in the older subset of subjects in the -023T trial. In subjects ≥ 40 years old, the proportion of current severity of sleepiness responders was 16.0% (8/50) with Combination and 37.0% (17/46) with Concurrent, p = 0.019.

From the December 20, 2006, approvable letter:

> The Agency considers that there is preliminary evidence that the proposed combination has an improved safety profile in subjects over the age of 40. To confirm this hypothesis, a new trial similar to 190343-023T in a population of subjects whose age ≥ 40 is recommended; both the dry mouth and sleepiness endpoints would be expected to show significance and the magnitude would be expected to be at least that observed in the patients ≥40 years old in study 190343- 023T.

Study 190342-024T submitted in this May 2, 2007, amendment was designed to address this deficiency by evaluating and comparing the safety of fixed combination BID with 0.2% Alphagan TID and 0.5% timolol BID given concurrently following ocular administration for 10 days in glaucoma and ocular hypertension patients.

For the primary endpoint, the proportion of current severity of Sleepiness Responders in -024T was significantly less with Combination (9.2%) than with Concurrent (19.3%), p < 0.001.

SUMMARY

By finding a significant between-group difference in the current severity of Sleepiness Responders (a clinically relevant endpoint associated with decreased reaction time and impaired cognitive performance), Allergan has demonstrated that the fixed combination, alternative dosing regimen would provide a useful product because the safety profile of the proposed combination product is better than that of the individual agents taken as currently permitted in the approved labeling. The combination's IOP-lowering ability is, however, inferior (approximately 1-2 mmHg) to that of brimonidine and timolol given concomitantly.

NDA 21-398 for Combigan (brimonidine tartrate/timolol maleate ophthalmic solution) 0.2%/0.5% is recommended for approval with the labeling revisions found in this review; the IOP-lowering of Combigan BID was slightly less than that seen with the concomitant administration of 0.5% timolol BID and 0.2% brimonidine TID.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

Individual safety and efficacy data is presented for each of the Phase 3 trials in either this review or in the four previous Medical Officer reviews.

For pooled common adverse event data tables, refer to the Medical Officer's review dated March 4, 2005, of the September 13, 2004, amendment.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The recommended dose is one drop of Combigan in the affected eye(s) twice daily. If more than one topical ophthalmic product is to be used, the different products should be instilled at least 5 minutes apart.

There is no recommendation for changing the dosing regimen for the combination product. See section 1.3.2 for dosing considerations.

8.2 Drug-Drug Interactions

Drug-drug interactions were not evaluated in this submission. There are theoretical reactions per the individual labels for brimonidine and timolol which are addressed in the revised labeling:

- Antihypertensives/Cardiac glycosides
- Beta-adrenergic blocking agents
- Calcium antagonists
- Catecholamine-depleting drugs
- CNS Depressants
- CYP2D6 inhibitors
- Tricyclic Antidepressants.

8.3 Special Populations

An evaluation of this use of this product in special populations was conducted in the original NDA review. There were no significant differences seen in the IOP lowering ability of the combination product in any of the subgroups analyzed. There were no gender, age or race effects on safety or efficacy with the use of the combination product.

8.4 Pediatrics

Per the revised product labeling:

[redacted] study in pediatric glaucoma patients (ages 2 to 7 years). In this study, brimonidine tartrate ophthalmic solution 0.2% was dosed TID as adjunctive therapy to beta-blockers. The most commonly observed adverse events were somnolence (50%-83% in patients 2 to 6 years) and decreased alertness. In pediatric patients 7 years of age or older (>20 kg), somnolence appears to occur less frequently (25%). Approximately 16% of patients on brimonidine tartrate ophthalmic solution discontinued from the study due to somnolence.

The safety and effectiveness of brimonidine tartrate and timolol maleate have not been studied in children below the age of 2 years. Combigan is not recommended for use in children under the age of 2 years. During post-marketing surveillance, apnea, bradycardia, hypotension, hypothermia, hypotonia, and somnolence have been reported in infants receiving brimonidine.

8.5 Advisory Committee Meeting

Not applicable. No advisory meeting was held for this drug product.

8.6 Literature Review

A literature search conducted by this reviewer failed to identify any literature references which were contrary to the information provided or referenced by Allergan in this application for this indication.

8.7 Postmarketing Risk Management Plan

There are no proposed risk management actions except the usual postmarketing collection and reporting of adverse experiences associated with the use of the drug product.

8.8 Other Relevant Materials

In a Division of Medication Errors and Technical Support (DMETS) review dated November 20, 2006, there were the following recommendations:

1. DMETS reverses its initial decision and does not recommend the use of the proprietary name, Combigan. This is considered a final decision.
2. DMETS recommends implementation of the label and labeling comments outlined in the review in order to minimize potential errors with the use of this product.

3. DDMAC finds the proprietary name "Combigan" acceptable from a promotional perspective.

In reviewing the proprietary name, Combigan, the primary concerns related to look-alike and sound-alike confusion with ComBgen and look-alike confusion with Lumigan.

Reviewer's Comments:

ComBgen is a prescription vitamin and mineral supplement containing Cyanocobalamin 500 mcg, Folic Acid 2.2 mg, and Pyridoxine 25 mg. ComBgen is usually prescribed as one tablet once daily or dosing may be based on individual needs as directed by a healthcare provider.

The differences between Combigan and ComBgen include dosage form (ophthalmic solution vs. oral tablet), product strength (0.2%/0.5% vs. 500 mcg/2.2 mg/25 mg), prescribed dose (one drop vs. one tablet), route of administration (ophthalmic vs. oral), dosing frequency (twice daily vs. once daily or as prescribed), package size (5 mL, 10 mL, or 15 mL vs. 100 count), and package configuration (dropper bottle vs. trade bottle).

This reviewer does not agree that substitution of this product with ComBgen is problematic

Lumigan is a prescription topical ophthalmic drop for the reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension. Substitution of Combigan with Lumigan would not be expected to have significant deleterious safety or efficacy consequences since both products have similar indications and efficacy in IOP lowering.

9 OVERALL ASSESSMENT

9.1 Conclusions

By finding a significant between-group difference in the current severity of Sleepiness Responders (a clinically relevant endpoint associated with decreased reaction time and impaired cognitive performance), Allergan has demonstrated that the fixed combination, alternative dosing regimen would provide a useful product because the safety profile of the proposed combination product is better than that of the individual agents taken as currently permitted in the approved labeling. The combination's IOP-lowering ability is, however, inferior (approximately 1-2 mmHg) to that of brimonidine and timolol given concomitantly.

9.2 Recommendation on Regulatory Action

NDA 21-398 for Combigan (brimonidine tartrate/timolol maleate ophthalmic solution) 0.2%/0.5% is recommended for approval with the labeling revisions found in the review; the IOP-lowering of Combigan BID was less than that seen with the concomitant administration of 0.5% timolol BID and 0.2% brimonidine TID, but the safety profile was improved.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

There are no proposed risk management actions except the usual postmarketing collection and reporting of adverse experiences associated with the use of the drug product.

9.3.2 Required Phase 4 Commitments

There are no recommended Phase 4 clinical study commitments.

9.3.3 Other Phase 4 Requests

There are no optional or recommended Phase 4 requests.

9.4 Labeling Review

See Section 10.2 for a line-by-line labeling review of package insert and carton and container labeling.

9.5 Comments to Applicant

The labeling changes found in this review should incorporated into the labeling for Combigan.

The established name on the carton and container labels should be revised to a font size that is at least half as large of that of the proprietary name and a prominence commensurate with the proprietary name, as stated in 21 CFR 201.10(g)(2).

10 APPENDICES

10.1 Review of Individual Study Reports

See Sections 6 and 7 for comments regarding -024T.

10.2 Line-by-Line Labeling Review

11 Page(s) Withheld

_____ Trade Secret / Confidential

__✓__ Draft Labeling

_____ Deliberative Process

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/s/

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