CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-398

SUMMARY REVIEW

Acting Division Director Memorandum
Wiley A. Chambers, MD
NDA 21-398 Combigan (brimonidine tartrate/timolol maleate ophthalmic solution)

Amended New Drug Application

Amendment Submission Dates:	May 2, and October 24 and 25, 2007
Review Completed:	October 25, 2007
Acting Division Director:	Wiley A. Chambers, MD
Established Name:	**Combigan** (brimonidine tartrate/timolol maleate ophthalmic solution) 0.2%/0.5%
Applicant:	Allergan Inc.
Pharmacologic Category:	Alpha-2 agonist/ Beta blocker
Proposed Indication:	Reduction of intraocular pressure
Dosage Form:	Ophthalmic solution
Route of Administration:	Topical ocular
NDA Drug Classification:	4S

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I. Recommendations

A. Recommendation on Approvability

Concurrence with the Medical Officer's Review dated September 19, 2007. NDA 21-398 is recommended for approval for lowering intraocular pressure in patients with [redacted] glaucoma or ocular hypertension because there are benefits contributed by each component and although the benefits would be greater if the two components are administered separately as labeled, the safety profile of the combination is superior to the two components administered separately as labeled. The final conclusion is based on the potential benefits of the combination outweighing the potential risks that each additional component adds to the combination.

B. Recommendation on Postmarketing Studies and/or Risk Management Steps

No postmarketing studies are recommended. No risk management steps are recommended.

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

Ocular hypertension is defined as high intraocular pressure (IOP) and may lead to optic nerve head abnormalities and visual field defects. Currently there is no proven direct treatment for optic neuropathy regardless of the initiating cause. Therapy is focused on lowering the intraocular pressure. Presently, five classes of drugs are used to reduce IOP: adrenergic beta-receptor antagonists; cholinergic agonists; adrenergic agonists, carbonic anhydrase inhibitors; and prostaglandin/prostaglandin analogs.

The new drug product proposed in this application is a combination of two of the classes of approved products (alpha 2 agonists and beta blockers).

The original NDA review for brimonidine tartrate 0.2%/timolol 0.5% ophthalmic solution concluded that sufficient evidence had not been presented to demonstrate that there was a contribution of each of the individual components to the overall affect of the drug as required by 21CFR 300.50. This amendment has been submitted in response to the approvable actions taken and contains the results of three clinical trials, 190342-023T, 190342-012T, and 190342-013T.

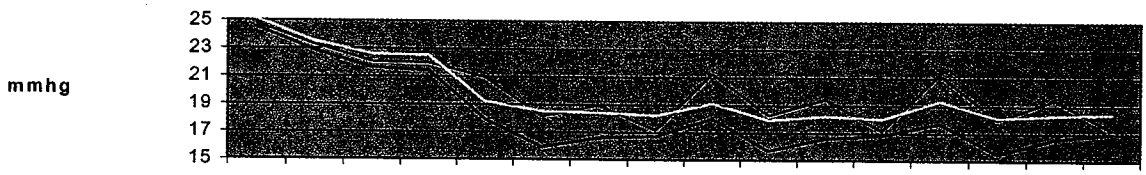
The 12 month clinical study reports for 190342-012T and 190342-013T are submitted here; the 3 month study reports for these protocols were included in the original NDA submission. There are no significant differences between the 3 month and 12 months results of studies 012 and 013.

190342-023T was designed to demonstrate 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.

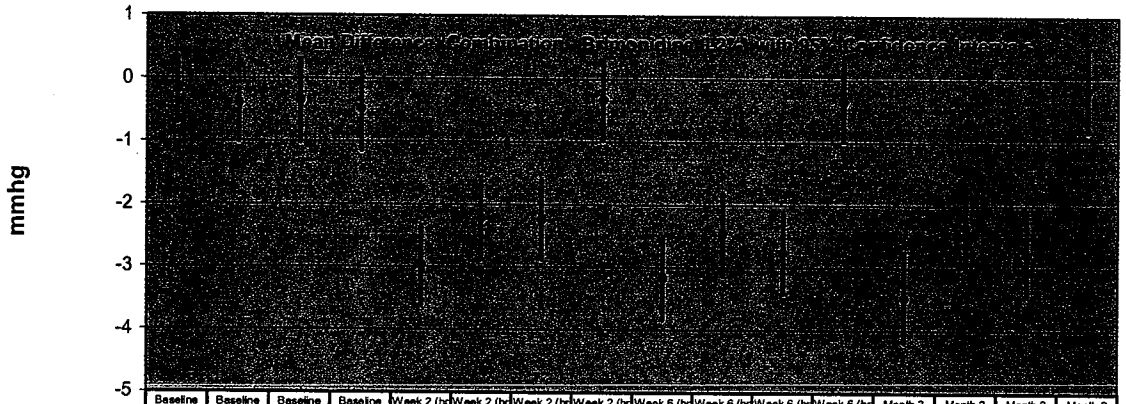
Study 190342-024T was submitted in May 2, 2007. The amendment was designed to address the deficiency identified in the approvable letter by evaluating and comparing the safety of fixed combination BID with 0.2% Alphagan TID and 0.5% timolol BID given concurrently following ocular administration for 10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

B. Efficacy

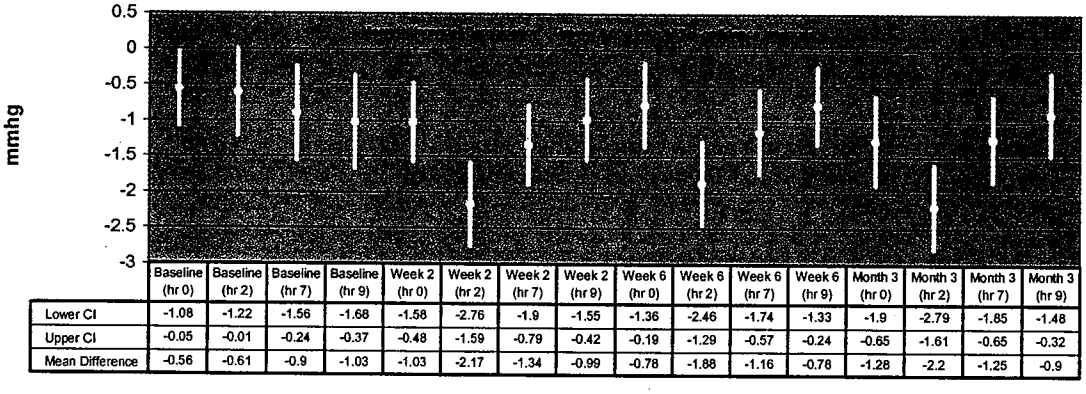
Mean Diurnal IOP - Study 012T



	Baseline (hr 0)	Baseline (hr 2)	Baseline (hr 7)	Baseline (hr 9)	Week 2 (hr 0)	Week 2 (hr 2)	Week 2 (hr 7)	Week 2 (hr 9)	Week 6 (hr 0)	Week 6 (hr 2)	Week 6 (hr 7)	Week 6 (hr 9)	Month 3 (hr 0)	Month 3 (hr 2)	Month 3 (hr 7)	Month 3 (hr 9)
Combination	24.5	22.8	21.6	21.4	17.9	16.9	16.6	16.7	18	16.7	16.6	16.8	17.7	16.5	16.6	17
Brimonidine 0.2%	24.7	23.2	22	21.9	20.9	18.1	18.9	17.1	21.2	18.2	19.4	17.1	21.2	17.9	19.4	17.2
Timolol 0.5%	25.1	23.6	22.6	22.5	19.2	18.5	18.4	18.2	19.1	17.9	18.2	18	19.3	18.1	18.3	18.4

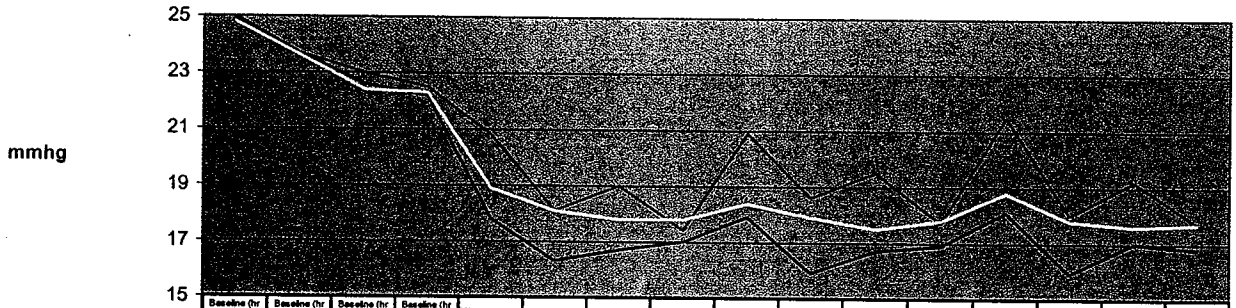


	Baseline (hr 0)	Baseline (hr 2)	Baseline (hr 7)	Baseline (hr 9)	Week 2 (hr 0)	Week 2 (hr 2)	Week 2 (hr 7)	Week 2 (hr 9)	Week 6 (hr 0)	Week 6 (hr 2)	Week 6 (hr 7)	Week 6 (hr 9)	Month 3 (hr 0)	Month 3 (hr 2)	Month 3 (hr 7)	Month 3 (hr 9)
Lower CI	-0.73	-1.03	-1.04	-1.17	-3.63	-2.9	-2.89	-1	-3.85	-3.15	-3.43	-1	-4.22	-3.05	-3.47	-0.84
Upper CI	0.31	-0.19	0.29	0.15	-2.36	-1.58	-1.62	0.28	-2.53	-1.82	-2.13	0.24	-2.77	-1.67	-2.12	0.48
Mean Difference	-0.21	-0.42	-0.38	-0.51	-2.99	-2.24	-2.26	-0.36	-3.19	-2.48	-2.78	-0.38	-3.5	-2.36	-2.8	-0.18

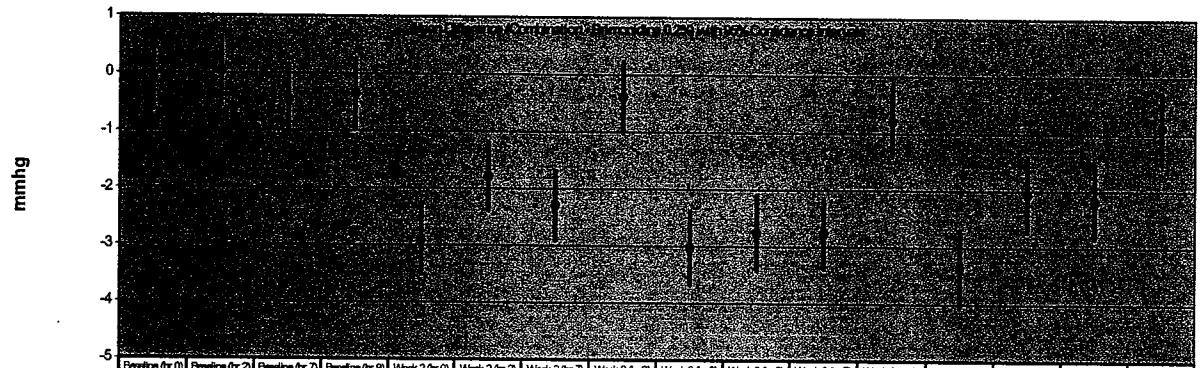


	Baseline (hr 0)	Baseline (hr 2)	Baseline (hr 7)	Baseline (hr 9)	Week 2 (hr 0)	Week 2 (hr 2)	Week 2 (hr 7)	Week 2 (hr 9)	Week 6 (hr 0)	Week 6 (hr 2)	Week 6 (hr 7)	Week 6 (hr 9)	Month 3 (hr 0)	Month 3 (hr 2)	Month 3 (hr 7)	Month 3 (hr 9)
Lower CI	-1.08	-1.22	-1.56	-1.68	-1.58	-2.76	-1.9	-1.55	-1.36	-2.46	-1.74	-1.33	-1.9	-2.79	-1.85	-1.48
Upper CI	-0.05	-0.01	-0.24	-0.37	-0.48	-1.59	-0.79	-0.42	-0.19	-1.29	-0.57	-0.24	-0.65	-1.61	-0.65	-0.32
Mean Difference	-0.56	-0.61	-0.9	-1.03	-1.03	-2.17	-1.34	-0.99	-0.78	-1.88	-1.16	-0.78	-1.28	-2.2	-1.25	-0.9

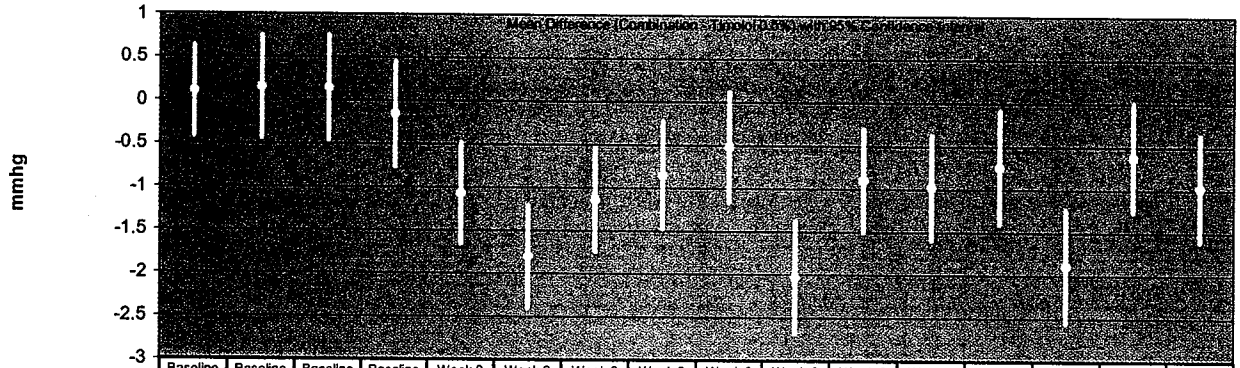
Mean Diurnal IOP - Study 013T



	Baseline (hr 0)	Baseline (hr 2)	Baseline (hr 7)	Baseline (hr 9)	Week 2 (hr 0)	Week 2 (hr 2)	Week 2 (hr 7)	Week 2 (hr 9)	Week 6 (hr 0)	Week 6 (hr 2)	Week 6 (hr 7)	Week 6 (hr 9)	Month 3 (hr 0)	Month 3 (hr 2)	Month 3 (hr 7)	Month 3 (hr 9)
Combination	24.9	23.7	22.6	22.2	17.6	16.3	16.7	17	17.9	15.9	16.7	16.9	16.1	15.9	17	16.6
Brimonidine 0.2%	25	23.7	23	22.5	20.6	18.1	19	17.4	20.9	18.6	19.5	17.7	21.5	18	19.2	17.7
Timolol 0.5%	24.8	23.6	22.4	22.3	18.9	18.1	17.8	17.5	18.4	17.9	17.5	17.6	18.8	17.8	17.6	17.7

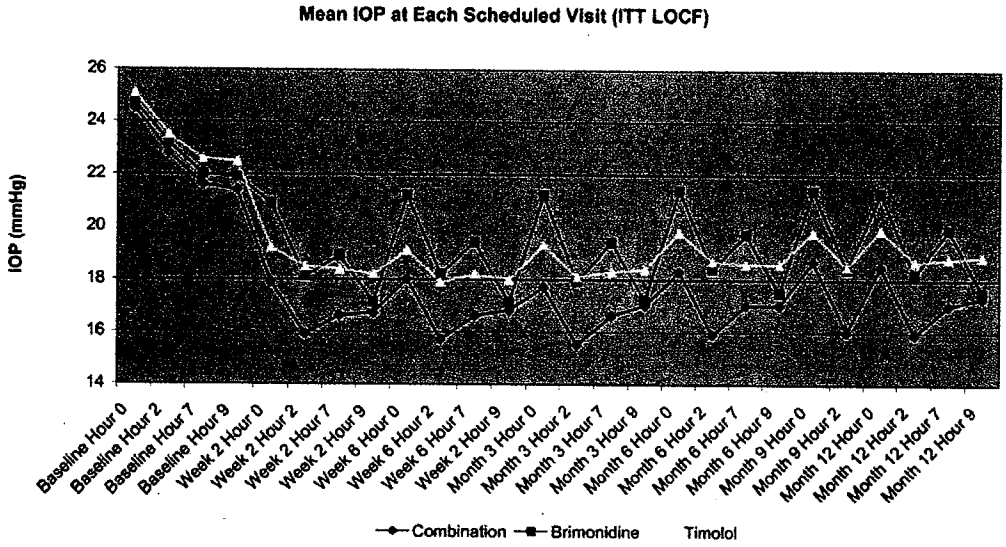


	Baseline (hr 0)	Baseline (hr 2)	Baseline (hr 7)	Baseline (hr 9)	Week 2 (hr 0)	Week 2 (hr 2)	Week 2 (hr 7)	Week 2 (hr 9)	Week 6 (hr 0)	Week 6 (hr 2)	Week 6 (hr 7)	Week 6 (hr 9)	Month 3 (hr 0)	Month 3 (hr 2)	Month 3 (hr 7)	Month 3 (hr 9)
Lower CI	-0.64	-0.56	-1.07	-0.98	-3.51	-2.4	-2.92	-1.03	-3.68	-3.42	-3.39	-1.41	-4.04	-2.74	-2.84	-1.53
Upper CI	0.42	0.62	0.14	0.25	-2.34	-1.21	-1.71	0.22	-2.4	-2.11	-2.19	-0.19	-2.72	-1.42	-1.58	-0.26
Mean Difference	-0.11	0.03	-0.47	-0.36	-2.92	-1.81	-2.31	-0.4	-3.04	-2.77	-2.79	-0.8	-3.36	-2.08	-2.21	-0.9

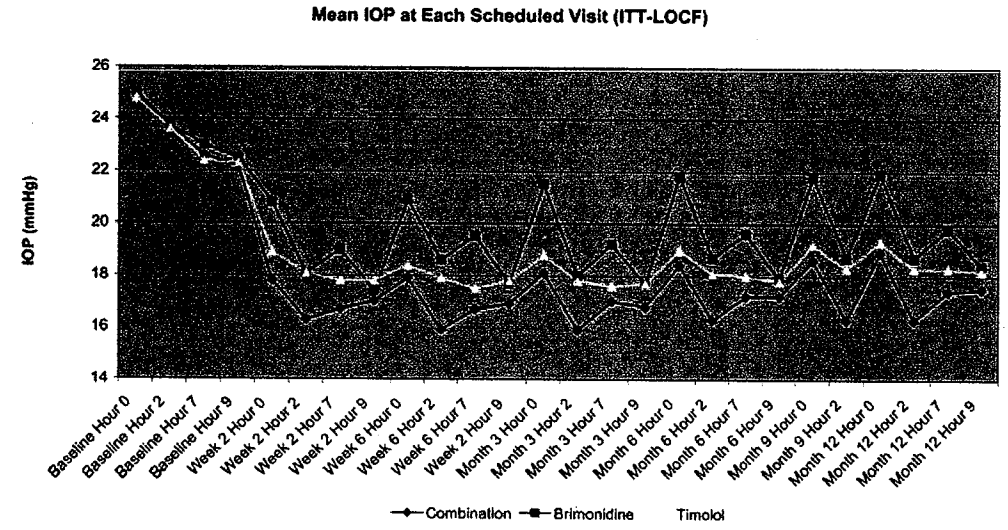


	Baseline (hr 0)	Baseline (hr 2)	Baseline (hr 7)	Baseline (hr 9)	Week 2 (hr 0)	Week 2 (hr 2)	Week 2 (hr 7)	Week 2 (hr 9)	Week 6 (hr 0)	Week 6 (hr 2)	Week 6 (hr 7)	Week 6 (hr 9)	Month 3 (hr 0)	Month 3 (hr 2)	Month 3 (hr 7)	Month 3 (hr 9)
Lower CI	-0.42	-0.44	-0.47	-0.77	-1.66	-2.41	-1.75	-1.48	-1.17	-2.69	-1.51	-1.6	-1.41	-2.56	-1.26	-1.61
Upper CI	0.63	0.74	0.75	0.45	-0.49	-1.22	-0.54	-0.24	0.11	-1.39	-0.31	-0.38	-0.09	-1.24	0	-0.37
Mean Difference	0.1	0.15	0.14	-0.16	-1.08	-1.81	-1.15	-0.86	-0.53	-2.04	-0.91	-0.99	-0.75	-1.9	-0.63	-0.99

Study 012



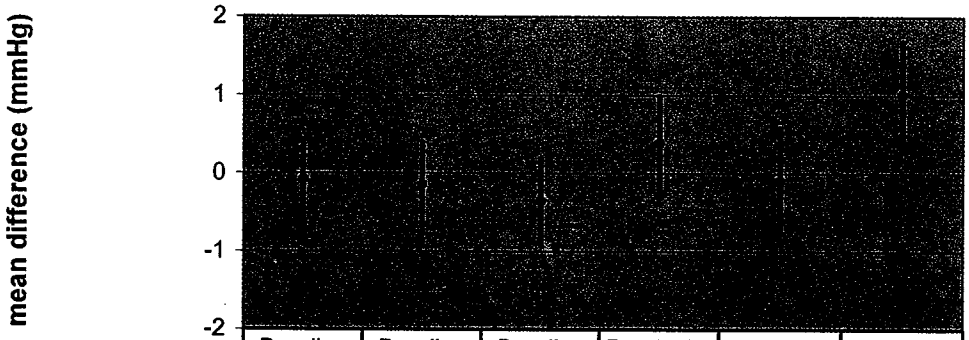
Study 013



Acting Division Director Memorandum
Wiley A. Chambers, MD
NDA 21-398 Combigan (brimonidine tartrate/timolol maleate ophthalmic solution)

Study 190342-019T

Mean Difference in IOP (combination-concurrent) with 95% Confidence Intervals



	Baseline (hr 0)	Baseline (hr 2)	Baseline (hr 8)	Day 28 (hr 0)	Day 28 (hr 2)	Day 28 (hr 8)
Lower CI	-0.57	-0.68	-0.91	-0.21	-0.78	0.33
Upper CI	0.42	0.39	0.19	0.99	0.58	1.69
• Mean Difference	-0.08	-0.15	-0.36	0.39	-0.1	1.01

vol 6, section 14.2, tables 14.2-1.1 and 14.2-1.2

IOP < 18 mmHg at All Time points - ITT Population

	Combination N=176	**Concurrent N=169**	**Alphagan N=87**	**Combination vs. Concurrent**	**Combination vs. Alphagan**	**Concurrent vs. Alphagan**
				p-values [a]		
Yes	63 (35%)	73 (43.2%)	13 (14.9%)	0.16	<0.001	<0.001

Vol 6, section 14.2, table 14.2-5

Comments: *The addition of brimonidine to timolol results in a minimal amount of additional IOP reduction (approximately 1 mmHg). The addition of timolol to brimonidine results in a minimal amount of additional IOP reduction (approximately 3 mmHg). The combination is slightly inferior to brimonidine and timolol being given concomitantly (approximately 0.19-1.69 mmHg). A slightly lower percentage of patients receiving the combination had all of their IOP measurements below 18 mmHg at all timepoints (35% versus 43%).*

C. Safety

Number of patients (%)	190342-012T and -013T Pooled 3-Month Data			190342-012T and -013T Pooled 12-Month Data			190342-019T			190342-506T			190342-507T	
	Comb	Brim	Timolol	Comb	Brim	Timolol	Comb	Concur	Brim	Comb	Brim	Timolol	Comb	Concur
	N = 385	N = 382	N = 392	N = 385	N = 382	N = 392	N = 174	N = 167	N = 85	N = 196	N = 202	N = 191	N = 188	N = 183
Body as a whole														
Infection	18 (4.7)	14 (3.7)	15 (3.8)	39 (10.1)	35 (9.2)	36 (9.2)	1 (0.6)	4 (2.4)	1 (1.2)	4 (2.0)	0c	0c	1 (0.5)	4 (2.2)
Asthenia	9 (2.3)	13 (3.4)	2 (0.5)[b]	11 (2.9)	17 (4.5)	3 (0.8)[b]	6 (3.4)	3 (1.8)	3 (3.5)	1 (0.5)	0	0	4 (2.1)	3 (1.6)
Accidental injury	3 (0.8)	3 (0.8)	3 (0.8)	11 (2.9)	5 (1.3)	10 (2.6)	0	0	0	0	0	0	0	0
Headache	8 (2.1)	11 (2.9)	5 (1.3)	9 (2.3)	16 (4.2)	9 (2.3)	5 (2.9)	6 (3.6)	2 (2.4)	3 (1.5)	2 (1.0)	0	12 (6.4)	14 (7.7)
Allergic reaction	2 (0.5)	6 (1.6)	3 (0.8)	7 (1.8)	12 (3.1)	5 (1.3)	0	1 (0.6)	0	0	1 (0.5)	0	0	0
Back pain	3 (0.8)	5 (1.3)	3 (0.8)	6 (1.6)	14 (3.7)	9 (2.3)	0	0	0	0	1 (0.5)	3 (1.6)	0	0
Flu syndrome	1 (0.3)	0	1 (0.3)	6 (1.6)	3 (0.8)	4 (1.0)	2 (1.1)	0	1 (1.2)	6 (3.1)	2 (1.0)	1 (0.5)	2 (1.1)	0
Cardiovascular														
Hypertension	10 (2.6)	7 (1.8)	5 (1.3)	25 (6.5)	13 (3.4)[a]	17 (4.3)	0	1 (0.6)	0	4 (2.0)	1 (0.5)	2 (1.0)	6 (3.2)	2 (1.1)
Digestive														
LFTs abnormal	4 (1.0)	2 (0.5)	3 (0.8)	10 (2.6)	3 (0.8)	8 (2.0)	0	0	0	2 (1.0)	0	1 (0.5)	1 (0.5)	0
Oral dryness	7 (1.8)	36 (9.4)[a]	2 (0.5)	8 (2.1)	36 (9.4)[a]	2 (0.5)	4 (2.3)	9 (5.4)	3 (3.5)	1 (0.5)	4 (2.0)	0	4 (2.1)	2 (1.1)
Nausea	3 (0.8)	2 (0.5)	1 (0.3)	8 (2.1)	4 (1.0)	2 (0.5)	1 (0.6)	1 (0.6)	1 (1.2)	0	0	0	1 (0.5)	0
Dyspepsia	2 (0.5)	3 (0.8)	5 (1.3)	6 (1.6)	5 (1.3)	10 (2.6)	0	0	0	1 (0.5)	0	1 (0.5)	0	0
Metabolic and Nutritional Disorders														
Hypercholesterolemia	1 (0.3)	1 (0.3)	1 (0.3)	14 (3.6)	4 (1.0)[a]	7 (1.8)	0	0	0	0	0	0	0	0
Diabetes mellitus	2 (0.5)	1 (0.3)	1 (0.3)	8 (2.1)	5 (1.3)	3 (0.8)	0	0	0	0	0	0	0	0
Peripheral edema	5 (1.3)	1 (0.3)	3 (0.8)	8 (2.1)	1 (0.3)[a]	4 (1.0)	1 (0.6)	1 (0.6)	0	0	0	0	1 (0.5)	1(0.5)
Musculoskeletal														
Arthritis	1 (0.3)	2 (0.5)	1 (0.3)	9 (2.3)	7 (1.8)	6 (1.5)	0	0	0	0	1 (0.5)	0	0	0
Depression	5 (1.3)	2 (0.5)	0[b]	9 (2.3)	5 (1.3)	1 (0.3)[b]	0	2 (1.2)	0	0	0	0	0	1 (0.5)
Somnolence	6 (1.6)	14 (3.7)	2 (0.5)	6 (1.6)	15 (3.9)[b]	2 (0.5)	0	2 (1.2)	2 (2.4)	4 (2.0)	4 (2.0)	1 (0.5)	4 (2.1)	3 (1.6)
Dizziness	5 (1.3)	6 (1.6)	6 (1.5)	5 (1.3)	6 (1.6)	7 (1.8)	0	1 (0.6)	2 (2.4)	1 (0.5)	3 (1.5)	3 (1.6)	1 (0.5)	1 (0.5)
Respiratory														
Bronchitis	3 (0.8)	3 (0.8)	1 (0.3)	9 (2.3)	7 (1.8)	3 (0.8)	0	2 (1.2)	0	1 (0.5)	1 (0.5)	0	1 (0.5)	2 (1.1)
Skin														
Rash	0	0	5 (1.3)	3 (0.8)	1 (0.3)	9 (2.3)	0	1 (0.6)	0	1 (0.5)	0	0	0	0
Special Senses														
Conjunctival hyperemia	32 (8.3)	39 (10.2)	21 (5.4)	66 (17.1)	90 (23.6)[a]	31 (7.9)[b]	2 (1.1)	1 (0.6)	0	9 (4.6)	9 (4.5)	4 (2.1)	7 (3.7)	7 (3.8)
Burning sensation in eye	38 (9.9)	21 (5.5)[a]	45 (11.5)	43 (11.2)	30 (7.9)	53 (13.5)	16 (9.2)	10 (6.0)	3 (3.5)	4 (2.0)	4 (2.0)	3 (1.6)	2 (1.1)	5 (2.7)
Stinging sensation in eye	21 (5.5)	7 (1.8)[a]	26 (6.6)	25 (6.5)	11 (2.9)[a]	27 (6.9)	9 (5.2)	6 (3.6)	0	0	0	0	0	0
Eye pruritus	9 (2.3)	25 (6.5)[a]	9 (2.3)	22 (5.7)	47 (12.3)[a]	15 (3.8)	1 (0.6)	0	1 (1.2)	2 (1.0)	7 (3.5)	3 (1.6)	9 (4.8)	5 (2.7)
Allergic conjunctivitis	4 (1.0)	17 (4.5)[a]	0	20 (5.2)	37 (9.7)[a]	2 (0.5)[b]	0	2 (1.2)	0	4 (2.0)	8 (4.0)[c]	0[c]	3 (1.6)	2 (1.1)
Conjunctival folliculosis	5 (1.3)	16 (4.2)[a]	2 (0.5)	19 (4.9)	35 (9.2)[a]	7 (1.8)[b]	0	0	0	3 (1.5)	6 (3.0)	1 (0.5)	2 (1.1)	0
Visual disturbance	16 (4.2)	16 (4.2)	7 (1.8)	18 (4.7)	18 (4.7)	16 (4.1)	6 (3.4)	6 (3.6)	0	3 (1.5)	3 (1.5)	3 (1.6)	4 (2.1)	7 (3.8)
Blepharitis	8 (2.1)	7 (1.8)	3 (0.8)	16 (4.2)	16 (4.2)	5 (1.3)[b]	0	0	0	3 (1.5)	1 (0.5)	0	0	0
Erythema eyelid	7 (1.8)	5 (1.3)	2 (0.5)	16 (4.2)	13 (3.4)	4 (1.0)[b]	1 (0.6)	0	0	1 (0.5)	2 (1.0)	0	1 (0.5)	0
Epiphora	7 (1.8)	10 (2.6)	5 (1.3)	14 (3.6)	20 (5.2)	7 (1.8)	1 (0.6)	0	0	4 (2.0)	0	2 (1.0)	4 (2.1)	3 (1.6)
Corneal erosion	9 (2.3)	6 (1.6)	5 (1.3)	14 (3.6)	7 (1.8)	13 (3.3)	1 (0.6)	0	0	1 (0.5)	0	2 (1.0)	0	0
Superficial punctate keratitis	6 (1.6)	5 (1.3)	3 (0.8)	14 (3.6)	5 (1.3)[a]	7 (1.8)	2 (1.1)	0	0	0	3 (1.5)	1 (0.5)	0	0
Eye dryness	7 (1.8)	9 (2.4)	2 (0.5)	12 (3.1)	14 (3.7)	5 (1.3)	0	2 (1.2)	0	2 (1.0)	2 (1.0)	0	1 (0.5)	0
Eye discharge	6 (1.6)	2 (0.5)	0[b]	12 (3.1)	9 (2.4)	4 (1.0)[b]	0	0	0	1 (0.5)	0	0	0	0
Eyelid edema	5 (1.3)	4 (1.0)	2 (0.5)	11 (2.9)	7 (1.8)	5 (1.3)	1 (0.6)	0	0	1 (0.5)	2 (1.0)	0	1 (0.5)	0
Foreign body sensation	7 (1.8)	14 (3.7)	7 (1.8)	8 (2.1)	19 (5.0)[a]	7 (1.8)	3 (1.7)	4 (2.4)	1 (1.2)	2 (1.0)	0	0	0	3 (1.6)
Eye pain	4 (1.0)	7 (1.8)	7 (1.8)	8 (2.1)	12 (3.1)	11 (2.8)	2 (1.1)	3 (1.8)	2 (2.4)	3 (1.5)	2 (1.0)	0	11 (5.9)	11 (6.0)
Irritation eye	1 (0.3)	2 (0.5)	3 (0.8)	8 (2.1)	3 (0.8)	5 (1.3)	0	2 (1.2)	0	0	1 (0.5)	2 (1.0)	2 (1.1)	0
Visual field defect	3 (0.8)	4 (1.0)	2 (0.5)	5 (1.3)	11 (2.9)	7 (1.8)	0	0	0	4 (2.0)	0[c]	0[c]	1 (0.5)	0
Cataract	2 (0.5)	1 (0.3)	1 (0.3)	4 (1.0)	10 (2.6)	7 (1.8)	0	0	1 (1.2)	0	0	2 (1.0)	1 (0.5)	0
Visual acuity worsened	2 (0.5)	2 (0.5)	3 (0.8)	4 (1.0)	5 (1.3)	10 (2.6)	4 (2.3)	2 (1.2)	0	2 (1.0)	1 (0.5)	0	1 (0.5)	2 (1.1)
Conjunctival edema	0	1 (0.3)	3 (0.8)	2 (0.5)	8 (2.1)	4 (1.0)	0	0	0	0	0	0	0	0
Follicular conjunctivitis	0	3 (0.8)	0	1 (0.3)	10 (2.6)[a]	0	0	0	0	2 (1.0)	0	0	0	0
Conjunctivitis	1 (0.3)	3 (0.8)	1 (0.3)	2 (0.5)	5 (1.3)	4 (1.0)	0	1 (0.6)	0	0	4 (2.0)[c]	0	0	2 (1.1)
Urogenital														
Urinary infection	4 (1.0)	4 (1.0)	1 (0.3)	10 (2.6)	9 (2.4)	5 (1.3)	0	0	0	1 (0.5)	2 (1.0)	0	0	0

Vol. 4, section 2.7.4, table 2.7.4.2-3
Comb = brimonidine tartrate 0.2%/timolol 0.5%; Timolol = timolol 0.5%; Brim = brimonidine tartrate 0.2%; Concur = concurrent brimonidine tartrate 0.2%/timolol 0.5%
[a] $p < 0.05$ for Combination vs. Brimonidine
[b] $p < 0.05$ for Combination vs. Timolol
[c] $p < 0.05$ for proportions among treatment groups

Study 023

Current Severity of Sleepiness
Proportion of Sleepiness Responders [MITT]

Combination	Concurrent	Difference (95% CI), p-value
N = 223	N = 227	
54/223 (24.2%)	68/227 (30.0%)	-5.7% (-13.9%, 2.5%), 0.179

Current Severity of Dry Mouth
Proportion of Dry Mouth Responders [MITT]

Combination	Concurrent	Difference (95% CI), p-value
N = 223	N = 227	
45/222 (20.3%)	68/227 (30.0%)	-9.7% (-17.7%, -1.7%), 0.016

SYSTEM ORGAN CLASS Preferred Term[a]	Combination N = 224	Concurrent N = 228	P-Value[b]
EYE DISORDERS			
eye irritation	17 (7.6%)	6 (2.6%)	0.016
dry eye	8 (3.6%)	7 (3.1%)	0.766
eye pruritus	6 (2.7%)	4 (1.8%)	0.541[c]
GASTROINTESTINAL DISORDERS			
dry mouth	6 (2.7%)	13 (5.7%)	0.109
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
fatigue	11 (4.9%)	17 (7.5%)	0.262
NERVOUS SYSTEM DISORDERS			
headache	21 (9.4%)	16 (7.0%)	0.361
somnolence	10 (4.5%)	13 (5.7%)	0.549

Source: Tables 14.3-9.1

a system organ class and preferred terms from the MedDRA nomenclature
b unless otherwise specified, p-value based on Pearson's chi-square test
c between-group p-value based on Fisher's exact test

Reviewer's Comments: *There is significant variability in the reported adverse events between the different studies. The combination is associated with all of the risks attributed to either of the individual ingredients. Timolol appears to slightly mask of some of the events attributed to brimonidine, but the potential masking of these events does not eliminate them and does not outweigh the decrease in IOP reduction seen in the afternoon. The systemic risks of timolol and brimonidine outweigh their potential benefit in the combination and for the equivalent risks seen with the concomitant; the efficacy is slightly decreased with the combination.*

Study 023 demonstrated a statistical difference in the percentage of dry mouth responders, but not in the percentage of sleepiness responders. A 10% difference in dry mouth responders and a minor improvement in ocular irritation upon instillation are not considered enough of a clinical difference to overcome the 1-2 mmHg difference in efficacy.

An exploratory analysis by age of the data was conducted and is demonstrated below.

Proportion of Current Severity of Sleepiness Responders by Age (mITT population in Study 023T)

Age Category	Combination	Concurrent	Relative Risk
≥ 20 years	24.1% (48/199)	32.3% (62/192)	1.3
≥ 25 years	23.7% (33/139)	33.1% (42/127)	1.4
≥ 30 years	19.8% (19/96)	31.9% (30/94)	1.6
≥ 35 years	17.5% (11/63)	34.8% (24/69)	2.0
≥ 40 years	16.0% (8/50) [a]	37.0% (17/46)	2.3
≥ 45 years	17.1% (7/41)	33.3% (11/33)	2.0
≥ 50 years	20.0% (5/25)	38.5% (5/13)	1.9

Source: study report 190342-023T, Table 14.6-19; Appendix Table 1
[a] P = 0.019 based on chi-square test

This analysis shows that a statistically significant difference in sleepiness responders could have been demonstrated if there had been older patients enrolled in the study.

Study 24

Study 190342-024T was a multi-center, randomized, parallel, double-blind trial. Patients were randomized 1:1 to either Combination or Concurrent therapy. The objective was to compare the safety of Combination with Concurrent therapy following ocular administration for 10 days in subjects with glaucoma or ocular hypertension. There were 604 treated subjects in the intent-to-treat (ITT) population for safety analysis with 304 subjects randomized to Combination therapy and 300 subjects to Concurrent therapy. There were 507 subjects included in the modified intent-to-treat (mITT) population.

The primary safety assessment variable was 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") for subjects in the ITT population. Secondary assessment variables included current severity of dry mouth (using a 5-point scale questionnaire with 1 being "note experiencing the symptom at all" and 5 being "intolerable"). 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) 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). The dry mouth scale had been validated against the risk of dental carries.

Severity of Symptom – Proportion of Responders

Symptom	Combination	Concurrent	RR (95% Confid)	P-value
Sleepiness	28/304 (9%)	58/300 (19%)	2.1 (1.4-3.2)	<0.001
Dry Mouth	45/304 (25%)	72/300 (24%)	1.6 (1.2-2.3)	0.005

Both sleepiness and dry mouth were found to be significant when comparing the combination product to concurrent use.

III. Reviews from Chemistry, Biopharmacology, Animal Pharmacology and Toxicology, DDMAC, Statistical, and/or Microbiology

Reviews have been completed from Chemistry/Manufacturing, Non-clinical Pharmacology/Toxicology, Biopharmaceutics, Statistics, Microbiology (sterility assurance), and Clinical Pharmacology. The Statistical Review has confirmed the analyses, but since there is no mathematical method to compare the efficacy and safety evaluations, this judgment has been deferred to the clinical team. There are no outstanding or unresolved issues from any of the reviews.

In a Division of Medication Errors and Technical Support (DMETS) review dated November 20, 2006, there were the following recommendations: DMETS reverses its initial decision and does not recommend the use of the proprietary name, Combigan. This is considered a final decision. 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. 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. I agree with the Review Division's Medical Officer. ComBgen is a 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). The product does not appear to be approved, nor is the labeling in compliance with Rx labeling requirements. I agree with the reviewer that substitution of this product with ComBgen is not likely.

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.

IV. 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.

V. Pediatrics

In response to a written request by the agency for brimonidine, the safety and effectiveness of the combination, administered as separate agents has been evaluated. The safety and effectiveness of Combigan in pediatric patients have not been established. Brimonidine tartrate ophthalmic solution 0.2% and ophthalmic beta blockers were evaluated in a well-controlled clinical 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.

VI. Advisory Committee Meeting

No advisory meeting was held for this drug product. Both components are approved as individual ingredients. There were no new issues identified in the review.

VII. 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.

VIII. Labeling

Labeling recommendations were summarized by the entire review team and forwarded to the applicant. The applicant has amended the application to include the labeling listed below. The review team is in agreement with the revised labeling.

8 Page(s) Withheld

_____ Trade Secret / Confidential

✓ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Medical-1

41 Page(s) Withheld

✓ Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Medical- 2

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