CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-490/S007

20-613/S018

21-262/S006

MEDICAL REVIEW

Medical Officer's Review of NDA 20-490/SE5-007,
NDA 20-613/SE5-018, and NDA 21-262/SE5-006
Pediatric Supplement

NDA 20-490/SE5-007, NDA 20-613/SE5-018, NDA 21-262/SE5-006 Medical Officer's Review	Submission Date: 08/14/2001 Review Completed: 10/04/01
Trademark:	ALPHAGAN® 0.5%, ALPHAGAN® 0.2%, and ALPHAGAN® P 0.15%
Generic Name:	Brimonidine tartrate ophthalmic solutions 0.5%, 0.2%, and 0.15%
Sponsor:	Allergan, Inc. 2525 Dupont Drive P.O. Box 19534 Irvine, CA 92623-9534 (800) 347-4500
Pharmacologic Category:	Alpha-2 adrenergic agonist
Indications:	Reduction of intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension (NDA 20-613 & NDA 21-262) Prevention of post-operative IOP elevation in patients undergoing argon laser trabeculoplasty (ALT) (NDA 20-490)
Dosage Form and Route of Administration:	Ophthalmic solution for topical ocular administration
NDA Drug Classification:	6P
Related IND:	[redacted]

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Executive Summary

II. Recommendations

A. It is recommended that supplemental NDA 20-490/SE5-007, NDA 20-613/SE5-018, and NDA 21-262/SE5-006 be approved. The sponsor adequately complied with all the requirements set forth in the pediatric written requested dated June 25, 1999. This submission demonstrates that brimonidine tartrate ophthalmic solution (ALPHAGAN®) is significantly associated with somnolence (25.0%-83.3%) and decreased alertness (beginning after 4 weeks of treatment) when used in the pediatric population ages 2 to 7 years. The clinical information should be included in the revised labels. Efficacy may be extrapolated from the database on older individuals.

II. Summary of Clinical Findings

A. Brimonidine tartrate ophthalmic solution (ALPHAGAN®) is a topical alpha-2 adrenergic agonist. ALPHAGAN®) 0.2% and ALPHAGAN® P 0.15% are indicated for the treatment of patients with open-angle glaucoma and ocular hypertension. ALPHAGAN® P 0.15% is a new formulation of brimonidine tartrate that contains purite as the preservative. ALPHAGAN® 0.5% is indicated for the prevention of post-operative IOP elevation in patients undergoing argon laser trabeculoplasty.

Agitation, apnea, bradycardia, convulsions, cyanosis, depression, dyspnea, emotional instability, hypotension, hypothermia, hypotonia, hypoventilation, irritability, lethargy, somnolence, and stupor have been reported in the pediatric population.

In response to a June 25, 1999, written request from the agency for pediatric information on brimonidine tartrate ophthalmic solution (NDA 20-490, NDA 20-613, and NDA 21-262), sponsor conducted a 3-month multicenter, randomized, double-masked, parallel group study that compared ALPHAGAN® 0.2% TID with TRUSOPT® 0.5% TID. It was the agency's view that efficacy data could be reliably extrapolated from the existing clinical database. Therefore, the primary objective of the written request was to obtain data on the safety and clinical response of brimonidine tartrate ophthalmic solution in the pediatric population.

B. Efficacy

The efficacy data (Protocol Study No. 190342-015) submitted with this submission was not adequately powered to demonstrate equivalence. Any analysis of the IOP lowering ability of brimonidine tartrate ophthalmic solution in the pediatric population based on this data is questionable. It is the agency's view

that efficacy data could be reliably extrapolated from the existing clinical database.

C. Safety

Somnolence was observed in every age strata from ages 2 to 7 years, ranging from 25.0% to 83.3% in subjects receiving Alphagan. Somnolence appears to occur with less frequency beginning age 7 years. Whereas, somnolence was not observed in any subjects receiving Trusopt. There also was a statistically significant difference in alertness between the two treatment groups as assessed by the investigators at weeks 4 and 8, and a significant difference at week 12. There was no difference between the two treatment groups in any of the other measured safety parameters including visual acuity, biomicroscopy, ophthalmoscopy, corneal diameter, and vital signs.

D. Dosing – N/A

E. Special Populations – N/A

Clinical Review

I. Clinical Background

A. Glaucoma is a common ophthalmologic disorder that is characterized by progressive optic nerve damage. Patients with open-angle glaucoma (OAG) typically experience an insidious loss of visual field that may progress to complete blindness.

The pathoetilogy of glaucoma is multifactorial; however, elevated intraocular pressure (IOP) is an accepted risk factor in the development and progression of the disease. The current standard of practice is the initiation and titration of pharmacologic agents to levels that safely and effectively decrease IOP.

Although brimonidine tartrate was found to be ineffective as an orally administered antihypertensive agent, studies performed using topically instilled ophthalmic preparations found that it effectively and safely decrease IOP. Brimonidine tartrate ophthalmic solution at a concentration of 0.2% was approved by the United States FDA on September 6, 1996, and is commercially available as ALPHAGAN® 0.2% for the treatment of patients with open-angle glaucoma (OAG) and ocular hypertension (OHT). Since that time it has been approved in 44 other countries.

Brimonidine tartrate ophthalmic solution (ALPHAGAN®) at a concentration of 0.5% was approved by the United States FDA in 1997 for the prevention of post-

operative IOP elevation in patients undergoing argon laser trabeculoplasty (ALT). ALPHAGAN® 0.5% has not been marketed since its approval.

A new formulation of brimonidine tartrate containing purite as the preservative was developed. ALPHAGAN® P (brimonidine tartrate ophthalmic solution) 0.15% was approved by the United States FDA on March 16, 2001 for the treatment of patients with OAG and OHT.

In response to a June 25, 1999, written request from the agency for pediatric information on brimonidine tartrate ophthalmic solution (NDA 20-490, NDA 20-613, and NDA 21-262), sponsor conducted a 3-month multicenter, randomized, double-masked, parallel group study that compared ALPHAGAN® TID with TRUSOPT® TID. It was the agency's view that efficacy data could be reliably extrapolated from the existing clinical database. Therefore, the primary objective of the written request was to obtain data on the safety and clinical response of brimonidine tartrate ophthalmic solution in the pediatric population.

II. Clinically Relevant Findings from Chemistry, Toxicology, Microbiology, Biopharmaceutics, Statistics, and/or Other Consultant Reviews – NA

III. Human Pharmacokinetics and Pharmacodynamics - NA

IV. Description of Clinical Data Sources

The materials reviewed include NDA 20-490/SE5-007 Volume 1, NDA 20-613/SE5-018 Volumes 37.1–37.20, and NDA 21-692/SE5-006 Volume 1.

Included in this medical officer's review is the evaluation of one clinical trial conducted at 15 clinical centers located in the United States (5), India (4), Brazil (2), Israel (2), Mexico (1), and Singapore (1). See Table 1 for a descriptive summary of clinical data sources.

Table 1 – Description of Clinical Data Sources

Protocol Number	Study Design	Treatment Duration	Patient Population	Treatment Groups	Dosing	No. Sites	No. Subjects Randomized/ Completed	Status
Phase III Studies								
Efficacy/Safety/ Tolerability 190342-015 US, India, Brazil, Israel, Mexico & Singapore	Multicenter, double-masked, randomized, active-controlled	3 months	Pediatric glaucoma patients on beta-blocker treatment	Alphagan 0.2% Trusopt 0.5%	TID TID	15 US (5) India (4) Brazil (2) Israel (2) Mexico(1) Singapore (1)	76/63 (1:1)	Completed

V. Clinical Review Methods

The primary objective in the review of these supplements (NDA 20-490, NDA 20-613, NDA 21-262) was to determine the safety profile and clinical response of Alphagan (brimonidine tartrate ophthalmic solution) in the pediatric population.

VI. Integrated Review of Efficacy

The purpose of these submissions was not to evaluate efficacy. It was the agency's view that efficacy data can be reliably extrapolated from the existing clinical database.

Clinical response data was collected. The results will be presented along with the safety data in the review of Protocol No. 190342-015 under Section VII.

VII. Integrated Review of Safety

Protocol No. 190342-015

Title:	A 3-Month, Multicenter, Randomized, Double-Masked, Parallel Comparison of the Safety, Efficacy, and Tolerability of ALPHAGAN® TID vs TRUSOPT TID as Adjunctive Treatment to Ophthalmic Beta-Blocker Treatment in Pediatric Glaucoma Patients
Objective:	To evaluate the safety, efficacy, and tolerability of Alphagan (brimonidine tartrate ophthalmic solution) in pediatric ($\geq$ 2 years and $\leq$7 years of age) glaucoma patients.

Study Design

This was a 3-month, multicenter, randomized, double-masked, active-controlled, parallel group comparison of Alphagan (brimonidine tartrate ophthalmic solution) 0.2% TID and Trusopt 0.5% TID (1:1 randomization) to evaluate the safety, efficacy, and tolerability when used with ophthalmic beta-blocker in pediatric ($\geq$ 2 years and $\leq$ 7 years of age) glaucoma patients. The two treatment groups were Alphagan 0.2% TID + ophthalmic beta-blocker and Trusopt 0.5% TID + ophthalmic beta-blocker.

Patients who met all eligibility criteria at the Pre-study visit underwent a 2-week (14 days) run-in period on an ophthalmic beta-blocker alone. After the 2-week run-in period, patients with glaucoma in at least one eye were randomized to receive either Alphagan 0.2% TID or Trusopt 0.5% TID. Patients with bilateral disease were treated with study medication in the worse eye for the first week followed by bilateral dosing for the remainder of the trial.

Approximately 75 patients were to be enrolled at 10-15 sites to obtain 60 completed cases. Enrolled patients were to be stratified by age to achieve equal distribution across the age groups.

Six follow-up visits (Pre-study, Day 0 (baseline and dosing starts), Week 1, Week 4, Week 8, Week 12) were scheduled for patients on unilateral dosing. Seven follow-up visits (Pre-study, Day 0 (baseline and worse eye dosing starts), Week 1 (bilateral dosing starts), Week 2, Week 4, Week 8, Week 12) were scheduled for patients on bilateral dosing.

Test Drug Schedule: Patients continued regular dosing regimen for current ophthalmic beta-blocker. Patients instilled one drop of masked study medication into each affected eye TID for 3 months.

Study Medications

Alphagan (Allergan Formulation Number 7831X) contains brimonidine tartrate 0.2% and benzalkonium chloride 0.005%, with purified water, polyvinyl alcohol, sodium chloride, sodium citrate, citric acid, and hydrochloric acid and/or sodium hydroxide to adjust pH.

Trusopt contains 20 mg/ml dorzolamide (22.3 mg of dorzolamide hydrochloride), benzalkonium chloride 0.0075%, hydroxyethyl cellulose, mannitol, sodium citrate dihydrate, sodium hydroxide to adjust pH, and water for injection.

Study Population

Inclusion Criteria

The following are requirements for entry into the study:

1. Male or female, 2 to 7 years of age (inclusive). Patients must enroll (Day 0) before his/her eighth birthday.

2. Patient has glaucoma (primary or secondary) in at least one eye and requires medication to lower intraocular pressure (IOP) in the affected eye(s).

3. Patient has been on ophthalmic beta-blocker monotherapy for at least 2 weeks prior to Pre-study and is in need of adjunctive treatment, **OR** patient has been on a beta-blocker and adjunctive treatment for at least 2 weeks prior to Pre-study and is either inadequately controlled or intolerant of current therapy (non-beta-blocker).

   Note that past glaucoma surgery is not an exclusion criterion providing the surgery was at least 3 months prior to study entry (baseline).

4. Patient can be on the ophthalmic beta-blocker alone for at least the 2-week run-in period (14 days, between Pre-study and Baseline visits) without putting the patient at significant risk.

   NOTE: Patients who are currently on ophthalmic beta-blocker monotherapy and who are inadequately controlled on such therapy will NOT be required to undergo the 14-day monotherapy run-in period.

5. In the investigator's opinion, patient's IOP is likely to be controlled with dual therapy.

6. Patient's IOP is likely to be reliably measured by a hand-held Tonopen™.

7. Minimum Vision Requirement: Patient must be able to at least fixate on and briefly follow a light or test object ("fix and follow").

8. Patient assent has been obtained (from children 7 years of age where required by regulatory authorities or local law), and Informed Consent has been obtained from parent or legally authorized representative.

9. Patient/Parent or legally authorized representative must be able to follow study instructions and likely to complete all required visits.

Exclusion Criteria

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

1. Previous or current history of unsuccessful treatment with a combination of a beta-blocker plus either ALPHAGAN® or TRUSOPT®.

2. Abnormally low or high blood pressure or heart rate.

3. Abnormally low body weight for age (below Lower Limit (5^{th} percentile)).

4. Known allergy or sensitivity to any of the study medication ingredients or diagnostic agents.

5. Contraindications to ALPHAGAN® such as concurrent use of monoamine oxidase (MAO) inhibitor therapy.

6. Contraindications to TRUSOPT® such as high-dose salicylate therapy.

7. Evidence of chronic corneal decompensation including corneal edema, bullous keratopathy or striate keratopathy.

Note: A well healed corneal scar or chronic Haab's striate alone will not exclude a patient.

8. History of penetrating keratoplasty in either eye.

9. Contraindications to sulfonamide therapy.

10. Contraindications to pupil dilation in either eye.

11. Any active ocular infection or inflammatory disease (e.g., uveitis, viral or bacterial infection).

12. Corneal abnormalities that would preclude accurate readings with a hand-held Tonopen™.

13. Any chronic seizure disorder or marked CNS deficit.

14. Any ocular surgery (including glaucoma surgery) within the 3 months prior to study entry (baseline).

15. Any condition or situation that, in the investigator's opinion, may put the patient at a significant risk, may confound study results, or may interfere significantly with patient's participation in the study.

16. Participation in a drug or device research study concurrently or within the 30 days (or longer if required by IRB/IEC) prior to entry into this study.

17. Anticipated wearing of contact lenses during the study.

Efficacy Variable

The primary efficacy variable of the study was IOP, evaluated using a hand-held Tonopen™. One IOP measurement was taken at approximately the same time at each study visit (Pre-study, Day 0 (Baseline), Week 1, Week 4, Week 8, Week 12).

The primary efficacy analysis focused on the mean change from baseline IOP at each measured time-point within each treatment group.

Safety Variables

Adverse events

Throughout the course of the study, all adverse events were monitored and reported on an adverse event case report form, including seriousness, severity, action taken and relationship to study drug. If adverse events occur, the first concern will be the safety of the study participants.

Ocular Measures
Visual Acuity: The best-corrected visual acuity at distance was measured for each eye using a LEA Symbols chart.

Biomicroscopy: Biomicroscopy was performed using slit lamp examination without pupil dilation. The examinations included evaluation of the condition of the lids, lid margins, conjunctiva, cornea, anterior chamber, lens, and vitreous. Observations were recorded using a 5-point scale (where 0 = none, 0.5 = trace, 1 = mild, 2 = moderate, and 3 = severe).

Ophthalmoscopy: The vitreous and fundus, including optic nerve head, were evaluated through a dilated pupil. Fundus pathology observations were made using a 5-point scale (where 0 = none, 0.5 = trace, 1 = mild, 2 = moderate, 3 = severe). Special notation was made of any abnormal findings.

Note: If the patient was not cooperative for any of the above procedures, a gross examination was performed instead.

Systemic Measures
Heart Rate: Heart rate was measured with patients in a resting state (seated) for approximately 5 minutes. Heart rate was counted over 30 seconds and multiplied by two and recorded in beats/minute.

Blood Pressure: Systolic/diastolic blood pressure was measured using a size appropriate pediatric pressure cuff with patients in a resting state (seated) for approximately 5 minutes. Blood pressure was recorded in mmHg.

Temperature: Temperature was measured using an oral thermometer. Temperature was recorded in °F or °C.

Respiration: Respiration rate was measured while patients were in a resting state. The number of breaths was counted over 30 seconds and multiplied by two and recorded in breaths/minute.

Alertness Evaluation: An alertness evaluation was performed by asking the parent/legally authorized representative a few questions based on the previous week. With those answers along with his/her clinical opinion, the investigator made an assessment of the patient's level of alertness using the following 6-point scale: Fully Alert; Alert; Lethargy; Obtunded; Stupor; Coma.

Other Measures
Corneal Diameter: The patient's estimated corneal diameter was measured using a near card.

Global Assessment of Success: The investigator evaluated the global assessment of success measured by a 4-point scale expressed by IOP-lowering efficacy, and general

safety and tolerability: Not Successful; Minimal Success; Moderate Success; Very Successful

Patient Comfort/Satisfaction, as Perceived by Parent or Legally Authorized-Representative Questionnaire: Patient satisfaction with previous anti-glaucoma medication(s) and with the study medication was assessed by his/her parent/legally-authorized representative. Parents/Legally authorized representative will rate their child's satisfaction using the following 7-point scale: Very Dissatisfied, Dissatisfied, Slightly Dissatisfied, Neither Satisfied nor Dissatisfied, Slightly Satisfied, Satisfied, Very Satisfied. Parents/Legally-authorized representatives will also rate their child's overall comfort using the following 6-point scale: Intolerable, Very Uncomfortable, Uncomfortable, Comfortable, Very Comfortable, Soothing.

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Table 2 – Schedule of Visits and Measurements

Study Period	Hour[a]	History and Consent	Vital Signs	VA	Alertness Evaluation	Corneal Diameter	IOP	Bio-microscopy	Ophthal-moscopy	Patient Comfort/ Satisfaction	Global Success Questionnaire
Pre-study (-14 days)	0	X	X	X		X	X	X	X	X	
14-day run-in period on ophthalmic beta-blocker alone [b]											
Day 0 (baseline)	0		X	X	X		X	X			
The first dose was administered immediately following the Day 0 (baseline), Hour 0 measurement											
	2[b]		X[c]		X[c]						
Week 1	0		X	X	X		X	X			
Patients with bilateral disease began dosing in the fellow eye immediately following the Week 1, Hour 0 measurement											
	2[c]		X[d]		X[d]						
Patients with bilateral disease only returned to the study site for a Week 2 follow-up											
Week 2	0		X		X						
Week 4	0		X	X	X		X	X			
Week 8	0		X	X	X		X	X			
Week 12 or Exit	0		X	X	X	X	X	X	X	X	X

[a] When possible, efforts were made to schedule all visits for the same time of day to assure consistency.
[b] Patients inadequately controlled on ophthalmic beta-blocker monotherapy were not required to undergo the 14-day run-in period.
[c] Patients remained in the office for at least 2 hours following the first dose administration.
[d] Patients remained in the office for at least 2 hours following the first bilateral dose.

Subject Disposition and Demographics

Table 3 – Subject Disposition

	Number of Subjects (%)		
	Alphagan	**Trusopt**	**Total**
Randomized	39 (50.6)	38 (49.4)	77
Enrolled	38 (50.0)	38 (50.0)	76 (98.7)
Completed Study	26 (68.4)	37 (97.4)	63 (82.9)
Discontinued Study	12 (31.6)	1 (2.6)	13 (17.1)

Table 4 – Discontinued Subjects and Reasons

Patient Number	Treatment	Age (years)	Weight (kg)	Reason
1435	Alphagan	6	19	Adverse events – cyanosis; headache; pallor; somnolence
1445	Alphagan	6	23	Lack of efficacy – high IOP and worse VA. Surgery was indicated.
1449	Alphagan	7	27	Other – mother withdrew consent due to somnolence.
1411	Alphagan	2	15	Adverse events – movement disorder; pallor; somnolence; tooth disorder
1416	Alphagan	7	21	Adverse event - somnolence
1146	Alphagan	7	25	Lack of efficacy
1323	Alphagan	5	16	Lack of efficacy – surgery was advised.
1325	Alphagan	5	13	Adverse event & lack of efficacy – lethargy; somnolence
1333	Alphagan	5	15	Lack of efficacy
1017	Alphagan	3	16	Adverse event - somnolence
1306	Alphagan	4	15	Lack of efficacy
1290	Alphagan	6	18	Other – improper entry
1374	Trusopt	6	18	Adverse events – fever; otitis media; paresthesia; seizure

Table 5 – Age Distribution

Age (years)	Alphagan (n=38)	Trusopt (n=38)	Total (n=76)
2	6 (15.8%)	5 (13.2%)	11 (14.5%)
3	4 (10.5%)	6 (15.8%)	10 (13.2%)
4	6 (15.8%)	5 (13.2%)	11 (14.5%)
5	6 (15.8%)	7 (18.4%)	13 (17.1%)
6	8 (21.1%)	8 (21.1%)	16 (21.1%)
7	8 (21.1%)	7 (18.4%)	15 (19.7%)

Table 6 - Summary of Demographic Characteristics (Intent-to Treat)

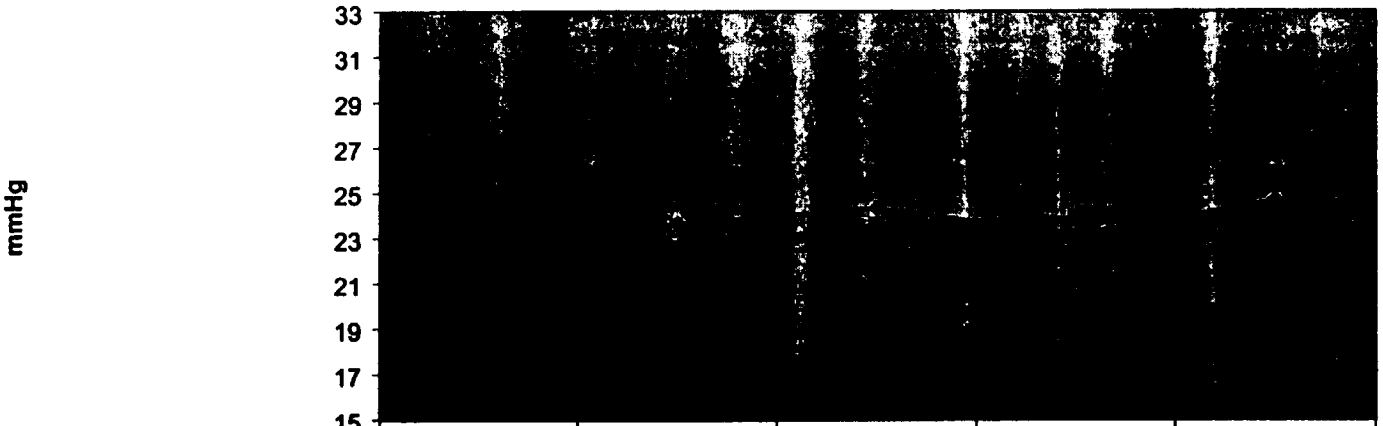
		Alphagan (n=38)	Trusopt (n=38)	Total (n=76)	P – value [a]
Age (years)	Mean	4.8	4.7	4.8	0.842
	SD	1.76	1.69	1.71	
	Median	5	5	5	
	Min	2	2	2	
	Max	7	7	7	
Sex	Male	25 (65.8%)	18 (47.4%)	43 (56.6%)	0.105
	Female	13 (34.2%)	20 (52.6%)	33 (43.4%0	
Race	Caucasian	30 (78.9%)	25 (65.8%)	55 (72.4%)	0.316
	Black	3 (7.9%)	8 (21.1%)	11 (14.5%)	
	Asian	0 (0.0%)	1 (2.6%)	1 (1.3%)	
	Hispanic	4 (10.5%0	4 (10.5%0	8 (10.5%)	
	Other [b]	1 (2.6%)	0 (0.0%)	1 (1.3%)	
Iris Color	Blue	3 (7.9%)	1 (2.6%)	4 (5.3%)	0.632
	Brown	29 (76.3%)	29 (76.3%)	58 (76.3%)	
	Green	0 (0.0%)	1 (2.6%)	1 (1.3%)	
	Hazel	2 (5.3%)	1 (2.6%)	3 (3.9%)	
	Dark Brown	4 (10.5%)	5 (13.2%)	9 (11.8%)	
	Other [c]	0 (0.0%)	1 (2.6%)	1 (1.3%)	
Weight (Kg)	Mean	17.64	17.48	17.56	0.883
	SD	4.455	4.929	4.667	
	Median	16.60	16.80	16.65	
	Min	9.5	10.0	9.5	
	Max	31.0	30.5	31.0	
Height (cm)	Mean	107.42	104.12	105.77	0.317
	SD	12.386	15.936	14.273	
	Median	104.50	105.66	105.16	
	Min	78.0	44.2	44.2	
	Max	132.0	134.0	134.0	

[a] P-value for age, weight and height was based on the 1-way ANOVA. Sex, race and iris color were analyzed by the Pearson chi-square or Fisher exact test.
[b] Other race: Mulatto. Indians are included in Caucasian group.
[c] Other iris color: aniridia

Efficacy - Protocol No. 190342-015 Intent-to-Treat Population

Primary Efficacy Variable

Mean IOP per Visit



	Baseline	Week 1	Week 4	Week 8	Week 12
Alphagan + Beta-blocker	29.38	23.66	24.31	23.11	24.64
Trusopt + Beta-blocker	30.37	22.58	23.57	23.89	25.84

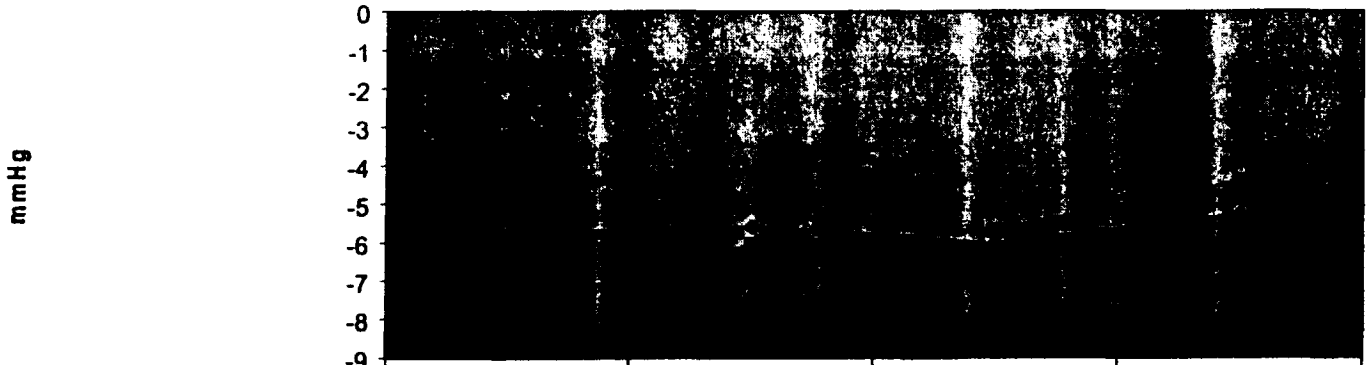
Reviewer's Comments: *Baseline mean IOP for Alphagan and Trusopt when used adjunctively with ophthalmic beta-blocker is similar. Alphagan 0.2% dosed TID and Trusopt 0.5% dosed TID when used adjunctively with ophthalmic beta-blocker demonstrate similar ability to lower IOP over visit days. Note: The study was not adequately powered to demonstrate equivalence. Any analysis comparing the IOP lowering ability of these two treatments groups is questionable.*

Mena Difference (Alphagan & beta-blocker - Trusopt & beta-blocker) with 95% CI

	Baseline	Week 1	Week 4	Week 8	Week 12
Lower CI	-5.34	-2.75	-3.53	-5.22	-5.1
Upper CI	3.36	4.9	5.01	3.66	2.71
■ Mean Difference	-0.99	1.07	0.74	-0.78	-1.19

Reviewer's Comments: *The mean IOP of the two treatment arms at baseline is comparable. The 95% confidence interval crosses zero at baseline. The mean difference between the mean IOP of Alphagan 0.2% dosed TID and Trusopt 0.5% dosed TID when used adjunctively with ophthalmic beta-blocker is not statistically significant at all time points measured and ranges from 1.07 to –1.19 mmHg. Note: The study was not adequately powered to demonstrate equivalence. Any analysis comparing the IOP lowering ability of these two treatment groups is questionable.*

Change in Mean IOP from Baseline by Visit



	Week 1	Week 4	Week 8	Week 12
Alphagan + Beta-blocker	-5.77	-5.59	-6.04	-5.29
Trusopt + Beta-blocker	-7.72	-6.06	-5.69	-4.41

Reviewer's Comments: *When corrected for baseline, the IOP lowering ability of Alphagan 0.2% and Trusopt 0.5% when used adjunctively with ophthalmic beta-blocker is similar. The change in mean IOP from baseline ranges from –5.29 to –6.04 mmHg for Alphagan 0.2% dosed TID and from –4.41 to –7.72 mmHg for Trusopt 0.5% dosed TID when used adjunctively with ophthalmic beta-blocker. Note: The study was not adequately powered to demonstrate equivalence. Any analysis comparing the IOP lowering ability of these two treatment groups is questionable.*

Safety

Adverse Events

All 76 subjects who enrolled in the study received at least one dose of study medication and were included in the safety analysis. Two serious adverse events occurred during the study, one (2.6%) in the Alphagan treatment group and one (2.6%) in the Trusopt treatment group. These serious adverse events resulted in the premature discontinuation one subject in the Trusopt treatment group. There were no deaths during the study.

The most common adverse events were somnolence (55.3%) and pharyngitis (13.2%) in the Alphagan treatment group and fever (15.8%) and infection (10.5%) in the Trusopt treatment group. Somnolence was reported in the Alphagan treatment group only and was reported in every age strata. Six subjects in the Alphagan treatment discontinued prematurely from the study due to somnolence.

Table 7 – Serious Adverse Events

Patient Number	Treatment	Coded Adverse Event	Outcome of Event	D/C from Study
1309	Alphagan	Cystitis	Resolved w/Tx	No
1374	Trusopt	Uncontrolled fever	Resolved w/Tx	Yes

Table 8 - Number (%) of Subjects with Adverse Events Occurring at Rates Greater than 1%

Coded Adverse Event	Alphagan N=38	Trusopt N=38
	N (%)	N (%)
All events	33 (86.8%)	25 (65.8%)
Body as a Whole		
Overall	14 (36.8%)	14 (36.8%)
Infection	4 (10.5%)	4 (10.5%)
Flu Syndrome	4 (10.5%)	3 (7.9%)
Fever	3 (7.9%)	6 (15.8%)
Headache	3 (7.9%)	2 (5.3%)
Allergic Reaction	1 (2.6%)	0 (0.0%)
Abdominal Pain	0 (0.0%)	2 (5.3%)
Abscess	0 (0.0%)	1 (2.6%)
Accidental Injury	0 (0.0%)	1 (2.6%)
Asthenia	0 (0.0%)	1 (2.6%)
Cardiovascular System		
Overall	2 (5.3%)	0 (0.0%)
Pallor	2 (5.3%)	0 (0.0%)
Digestive System		
Overall	3 (7.9%)	4 (10.5%)
Diarrhea	1 (2.6%)	2 (5.3%)

Coded Adverse Event	Alphagan N=38	Trusopt N=38
Vomiting	1 (2.6%)	2 (5.3%)
Tooth Disorder	1 (2.6%)	1 (2.6%)
Anorexia	1 (2.6%)	0 (0.0%)
Nausea	0 (0.0%)	1 (2.6%)
Heme and Lymphatic System		
Overall	1 (2.6%)	0 (0.0%)
Cyanosis	1 (2.6%)	0 (0.0%)
Metabolic and Nutritional Disorders		
Overall	0 (0.0%)	1 (2.6%)
Dehydration	0 (0.0%)	1 (2.6%)
Nervous System		
Overall	22 (57.9%)	4 (10.5%)
Somnolence	21 (55.3%)	0 (0.0%)
Insomnia	2 (5.3%)	2 (5.3%)
Nervousness	1 (2.6%)	1 (2.6%)
Movement Disorder	1 (2.6%)	0 (0.0%)
Hostility	0 (0.0%)	1 (2.6%)
Paresthesia	0 (0.0%)	1 (2.6%)
Seizure	0 (0.0%)	1 (2.6%)
Respiratory System		
Overall	8 (21.1%)	5 (13.2%)
Pharyngitis	5 (13.2%)	1 (2.6%)
Cough Decreased	3 (7.9%)	2 (5.3%)
Asthma	1 (2.6%)	1 (2.6%)
Hyperventilation	1 (2.6%)	0 (0.0%)
Infection Sinus	1 (2.6%)	0 (0.0%)
Infection	0 (0.0%)	1 (2.6%)
Rhinitis	0 (0.0%)	1 (2.6%)
Special Senses		
Overall	6 (15.8%)	14 (36.8%)
Conjunctival Hyperemia	2 (5.3%)	2 (5.3%)
Visual Acuity Worsened	2 (5.3%)	1 (2.6%)
Burning Sensation in Eye	1 (2.6%)	3 (7.9%)
Intraocular Pressure	1 (2.6%)	1 (2.6%)
Otitis Media	1 (2.6%)	1 (2.6%)
Cornea (NOS)	0 (0.0%)	2 (5.3%)
Anterior Synechia	0 (0.0%)	1 (2.6%)
Blepharitis	0 (0.0%)	1 (2.6%)
Conjunctival Folliculosis	0 (0.0%)	1 (2.6%)
Conjunctivitis	0 (0.0%)	1 (2.6%)
Corneal Edema	0 (0.0%)	1 (2.6%)
Corneal Erosion	0 (0.0%)	1 (2.6%)
Epiphora	0 (0.0%)	1 (2.6%)
Eye Pain	0 (0.0%)	1 (2.6%)
Papillary Hypertrophy	0 (0.0%)	1 (2.6%)
Superficial Punctate Keratitis	0 (0.0%)	1 (2.6%)
Urogenital System		
Overall	1 (2.6%)	0 (0.0%)
Cystitis	1 (2.6%)	0 (0.0%)
Hematuria	1 (2.6%)	0 (0.0%)

Table 9 – Frequency of Somnolence by Treatment and Age

Age (years)	Treatment		
	Alphagan	Trusopt	Total
2	3/6 (50.0%)	0 (0.0%)	3
3	3/4 (75.0%)	0 (0.0%)	3
4	4/6 (66.7%)	0 (0.0%)	4
5	5/6 (83.3%)	0 (0.0%)	5
6	4/8 (50.0%)	0 (0.0%)	4
7	2/8 (25.0%)	0 (0.0%)	2
	21/38 (55.3%)	0/38 (0.0%)	21/76 (27.6%) Total

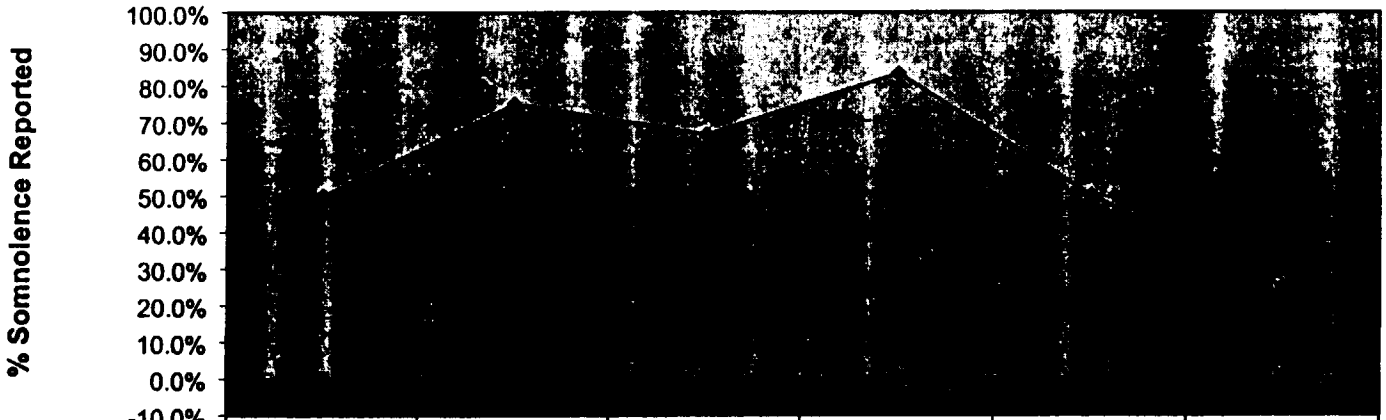
Table 10 – Frequency of Somnolence by Treatment and Weight

Weight (kg)	Treatment		
	Alphagan	Trusopt	Total
0-2	0/0 (0.0%)	0/0 (0.0%)	0
3-5	0/0 (0.0%)	0/0 (0.0%)	0
6-8	0/0 (0.0%)	0/0 (0.0%)	0
9-11	1/1 (100.0%)	0/3 (0.0%)	1
12-14	6/9 (66.7%)	0/10 (0.0%)	6
15-17	10/14 (71.4%)	0/10 (0.0%)	10
18-20	2/6 (33.3%)	0/5 (0.0%)	2
21-23	1/4(25.0%)	0/5 (0.0%)	1
24-26	1/3 (33.3%)	0/4 (0.0%)	1
27-29	0/0 (0.0%)	0/0 (0.0%)	0
30-32	0/1 (0.0%)	0/1 (0.0%)	0
	21/38 (55.3%)	0/38 (0.0%)	21/76 (27.6%) Total

Table 11 – Discontinued Subjects Due to Somnolence

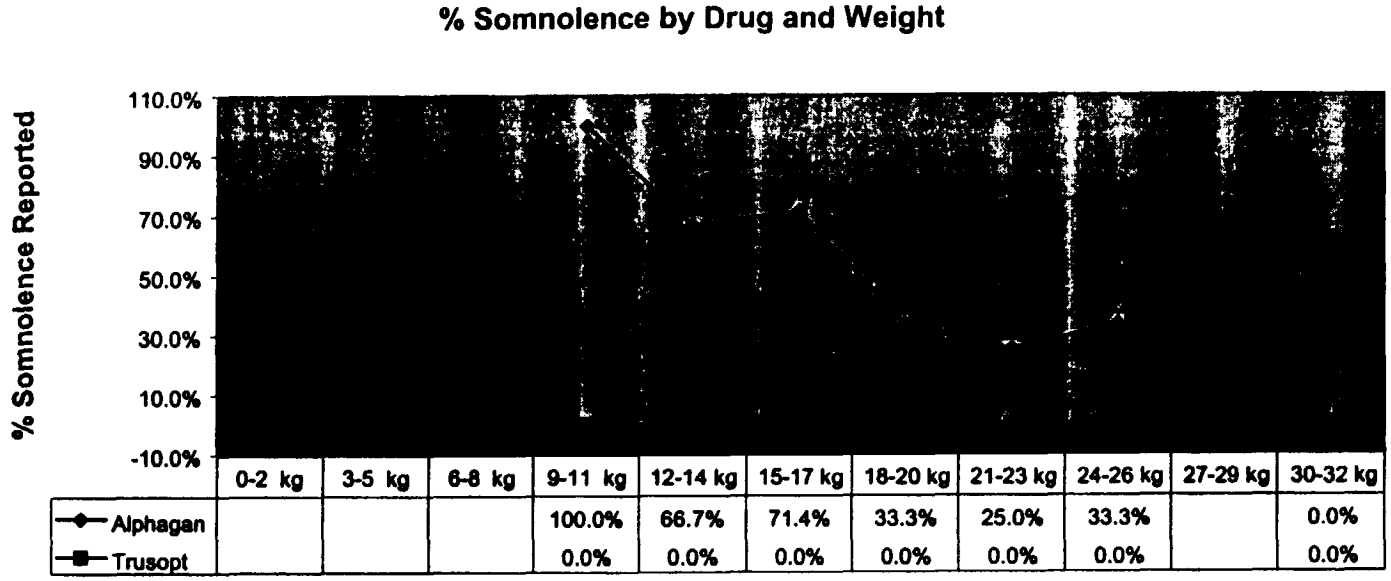
Patient Number	Treatment	Age (years)	Weight (kg)
1435	Alphagan	6	19
1449	Alphagan	7	27
1411	Alphagan	2	15
1416	Alphagan	7	21
1325	Alphagan	5	13
1017	Alphagan	3	16

% Somnolence by Drug and Age



	2 years	3 years	4 years	5 years	6 years	7 years
Alphagan	50.0%	75.0%	66.7%	83.3%	50.0%	25.0%
Trusopt	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%

Reviewer's Comments: *Somnolence was observed in every age strata, from ages 2 years to 7 years for the Alphagan treatment arm and ranged from 25.0% to 83.3%. Somnolence was not observed in any subjects treated with Trusopt.*



	0-2 kg	3-5 kg	6-8 kg	9-11 kg	12-14 kg	15-17 kg	18-20 kg	21-23 kg	24-26 kg	27-29 kg	30-32 kg
Alphagan				100.0%	66.7%	71.4%	33.3%	25.0%	33.3%		0.0%
Trusopt				0.0%	0.0%	0.0%	0.0%	0.0%	0.0%		0.0%

Reviewer's Comment: *Somnolence was observed in subjects weighing between 9 and 26 kg in the Alphagan treatment arm. The weight of subjects in the Alphagan treatment arm ranged from 9.5 to 31.0 kg. Somnolence was not observed in any subjects treated with Trusopt. The weight of subjects in the Trusopt treatment arm ranged from 10.0 to 30.5 kg.*

Ocular Measures

Visual Acuity

Change in visual acuity in the study eye was analyzed by determining change in line numbers, comparing the subject's final evaluation to baseline.

At the final visit, there were no statistical differences between treatment groups ($p > 0.999$).

Visual acuity using LEA symbols could not be tested in 2.9 % (11/38) of the patients in the Alphagan treatment group and 4.2 % (16/38) of the patients in the Trusopt treatment group due to either their age or poor vision (count finger or hand motion vision).

Table 12 – Change in Visual Acuity (LEA Symbols) from Baseline to Final Visit

	Treatment		
Line Changes	Alphagan N=38	Trusopt N=38	Total N=76
N	27 (71.1%)	22 (57.9%)	49 (64.5%)
≥ 2 lines loss	4 (14.8%)	2 (9.1%)	6 (12.2%)
1 line loss	2 (7.4%)	0 (0.0%)	2 (4.1%)
No change	11 (40.7%)	17 (77.3%)	28 (57.1%)
1 line gain	6 (22.2%)	1 (4.5%)	7 (14.3%)
≥ 2 lines gain	4 (14.8%)	2 (9.1%)	6 (12.2%)

Biomicroscopy and Ophthalmoscopy

The number and percent of patients with at least 1 severity grade increase in any biomicroscopy or ophthalmoscopy finding at 1 or more visits was tabulated.

There were no statistically significant differences between treatment groups in any of the biomicroscopy or ophthalmoscopy findings ($p=0.200$ to $p>0.999$).

Table 13 – Number (Percent) of Subjects with ≥ 1 Severity Grade Increase in Biomicroscopy and Ophthalmoscopy Finding from Baseline at ≥ 1 Visits

	Treatment		
Finding	Alphagan (N=38)	Trusopt (N=38)	P-value
Haab's Striae	9 (23.7%)	7 (18.4%)	0.574
Cornea Other	4 (10.5%)	3 (7.9%)	>0.999
Conjunctival Erythema	4 (10.5%)	2 (5.3%)	0.674
Conjunctiva Other	3 (7.9%)	3 (7.9%)	>0.999
Lens Pigment	3 (7.9%)	1 (2.6%)	0.615
Opacity (Cornea)	2 (5.3%)	1 (2.6%)	>0.999
Corneal Edema	2 (5.3%)	2 (5.3%)	>0.999
Bleb (Conjunctiva)	1 (2.6%)	5 (13.2%)	0.200
Iris Other	1 (2.6%)	2 (5.3%)	>0.999

Cataract	1 (2.6%)	5 (13.2%)	0.200
Nuclear Cataract	1 (2.6%)	1 (2.6%)	>0.999
Lens Pathology	1 (2.6%)	1 (2.6%)	>0.999
Fundus Pathology	1 (2.6%)	0 (0.0%)	>0.999
Anterior Chamber Anterior Synechiae	1 (2.6%)	1 (2.6%)	>0.999
Anterior Chamber Posterior Synechiae	1 (2.6%)	0 (0.0%)	>0.999
Lid Other	0 (0.0%)	1 (2.6%)	>0.999
Discharge (Conjunctiva)	0 (0.0%)	1 (2.6%)	>0.999
Endothelial Dystrophy	0 (0.0%)	1 (2.6%)	>0.999
Pannus (Corneal)	0 (0.0%)	1 (2.6%)	>0. 999
Scar (Cornea)	0 (0.0%)	2 (5.3%)	0.493
Band Shaped Keratopathy	0 (0.0%)	1 (2.6%)	>0.999
Anterior Chamber	0 (0.0%)	1 (2.6%)	>0.999
Optic Nerve Other	0 (0.0%)	1 (2.3%)	>0.999
Corneal Staining/Erosion	0 (0.0%)	2 (5.3%)	0.493

Systemic Measures

Heart rate, systolic and diastolic blood pressure, temperature, and respiratory rate were evaluated.

Reviewer's Comments:

There were no clinically significant difference in heart rate, blood pressure, temperature, and respiratory rate.

Alertness Evaluation

An alertness evaluation was made by asking parent/legally-authorized representatives questions about the subject's behavior during the previous week. Using the answers to these questions and their own opinion, investigators graded the subject's level of alertness on a 6-point scale (fully alert, alert, lethargic, obtunded, stupor, coma). When grading, investigators reported the lowest level of alertness during the previous week.

The difference in alertness between treatments groups was statistically significant at the weeks 4 and 8 visits (p=0.037 and p=0.032, respectively). P-value was not calculated for the week 12 visit. At the week 4 visit, 78.8% (26/33) of subjects in the Alphagan treatment group versus 100.0% (36/36) of the subjects in the Trusopt treatment group were observed as fully alert. At the week 8 visit, 75.9% (22/29), 13.8% (4/29), and 10.3% (3/29) of the subjects in the Alphagan treatment group were observed to be fully alert, alert, and lethargic, respectively as compared to 97.1% (34/35), 2.9% (1/35), 0.0% (0/35), respectively for subjects treated with Trusopt. At the week 12 visit, 79.3% (23/29), 13.8% (4/29), and 6.9% (2/29) of the subjects in the Alphagan treatment group

were observed to be fully alert, alert, and lethargic, respectively as compared to 97.3% (36/37), 2.7% (1/37), and 0.0% (0/37), respectively for subjects treated with Trusopt.

Other Measures

Corneal Diameter

Changes in corneal diameter were analyzed by determining changes in diameter, comparing subject's final evaluation to baseline.

At the final visit, there were no statistically significant differences between treatment groups (p=0.150). Within the Alphagan treatment group, the mean change from baseline corneal diameter was statistically significant (p=0.009).

Table 14 – Mean Change in Corneal Diameter from Baseline to Final Visit

		Treatment		
Timepoint		Alphagan (N=38)	Trusopt (N=38)	P-value[a]
Baseline	N	38	37	0.208
	Mean	12.6	13.0	
	SD	1.84	1.28	
	Median	13.0	13.0	
	Min			
	Max			
Week 12	N	38	37	0.150
	Mean	2.1	0.7	
	SD	4.76	3.29	
	Median	0.0	0.0	
	Min			
	Max			
	P-value[b]	0.009	0.182	

[a] P-value for between group comparison based on the 1-way analysis of variance.
[b] P-value for within-group analysis of changes from baseline using paired t-test.

Global Assessment of Success

Investigators were asked to assess "global success" of the treatments. "Global assessment of success" was defined as a combination of IOP-lowering efficacy and general safety and tolerability and was rated on a 4-point scale.

There was no statistically significant difference between treatment groups (p=0.199).

Patient Comfort/Satisfaction

Patient comfort with the previous glaucoma regimen (including the beta-blocker) and with study medications was rated on a 6-point scale ranging from soothing to intolerable.

Patients (and when not possible, parents for their children) rated the comfort of the previous regimen (baseline) and the study medications (final visit).

At baseline, patient comfort was comparable between treatment groups (p=0.210). There was no statistically significant difference between treatment groups at the final visit (p=0.829).

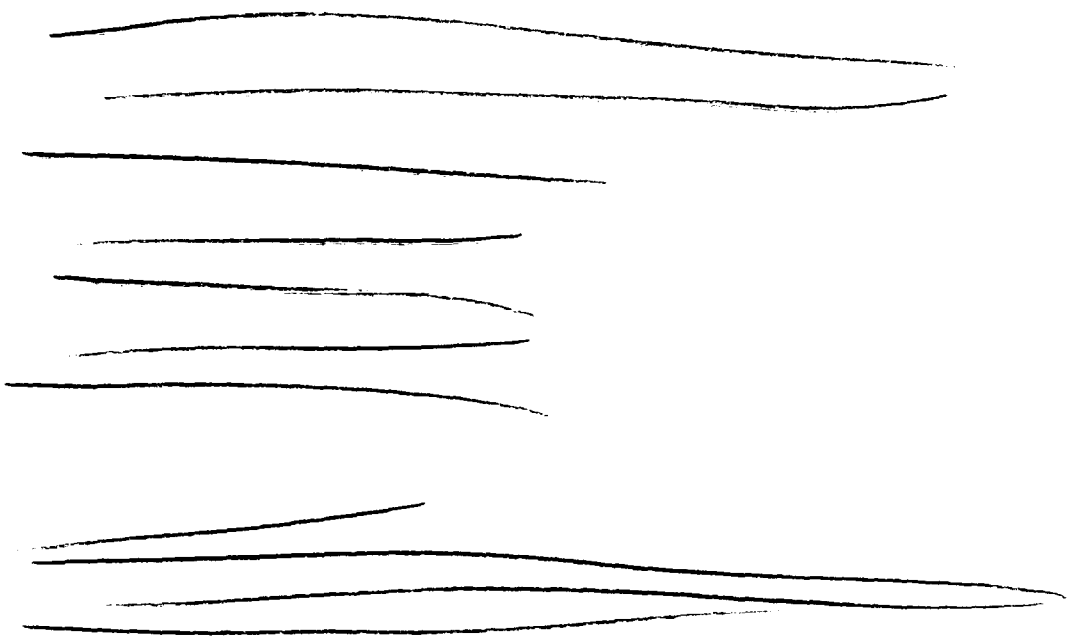
Patient satisfaction with the study medications was rated on a 7-point scale ranging from very satisfied to very dissatisfied. Patients (and when not possible, parents for their children) rated their satisfaction of the study medications at the final visit.

There was no statistically significant difference between treatment groups (p=0.120).

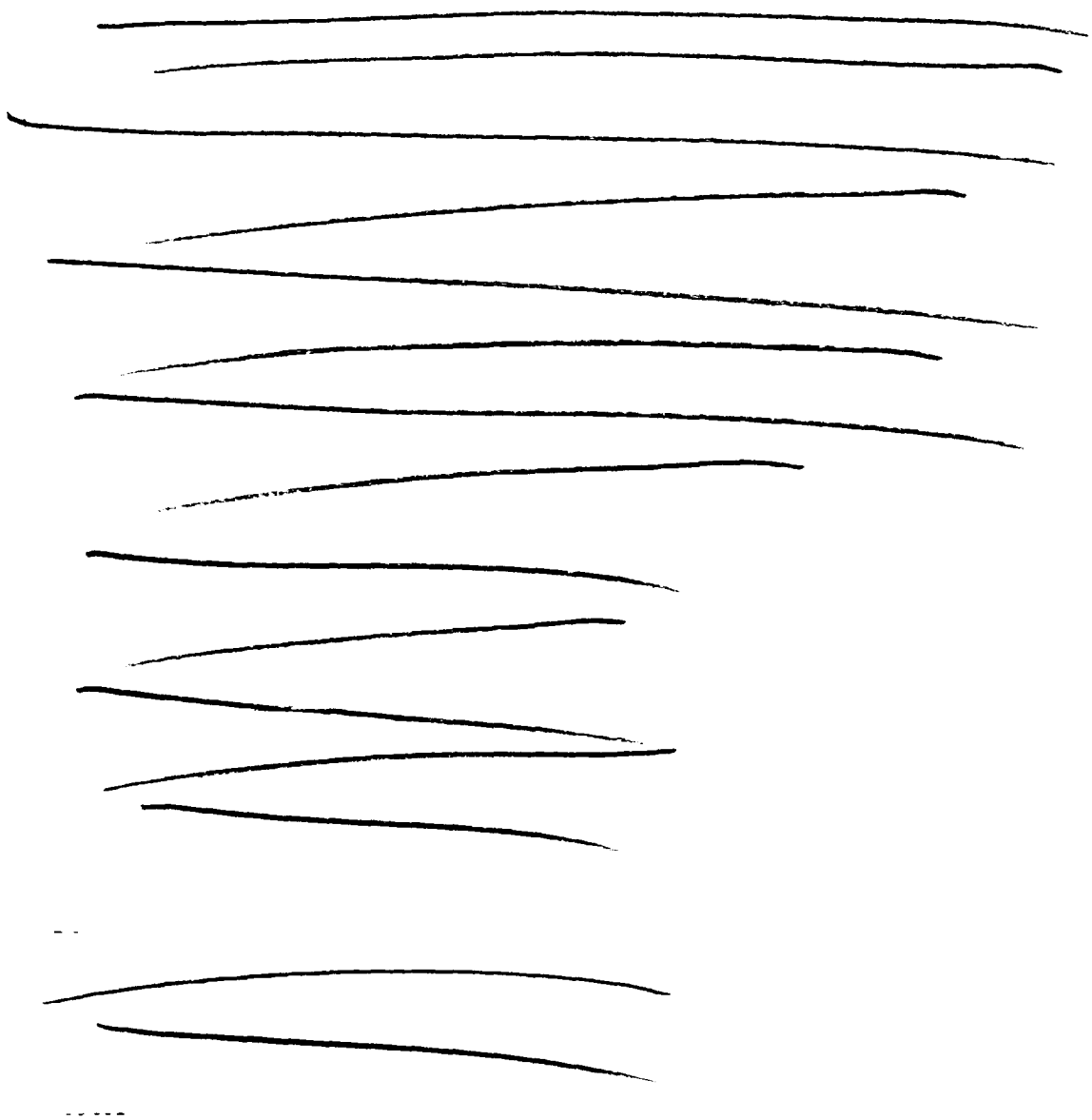
VII Dosing, Regimen, and Administration Issues – N/A

IX Use in Special Populations – N/A

X Labeling



13 page(s) of revised draft labeling has been redacted from this portion of the review.



IX Conclusions and Recommendations

Conclusions

This submission demonstrates that somnolence and decreased alertness are significantly associated with the use of Alphagan in the pediatric population ages 2 to 7 years, when dosed one drop to the affected eye(s) TID. Somnolence appears to occur with less frequency beginning age 7 years.

Recommendations

Supplemental NDA 20-490/SEE5-007, NDA 20-613/SE5-018, and NDA 21-262/SE5-006 is recommended for approval for use in the pediatric population ≥ 2 years of age with the revised labeling contained in this review.

Lucious Lim, M.D., M.P.H.
Medical Officer

NDA 20-490, NDA 20-613 & NDA 21-262
HFD-550/Div Files
HFD-550/MO/Lim
HFD-550/Biopharm/Bashaw
HFD-550/Biostats/Lin
HFD-550/Chem/Rodriguez
HFD-550/Pharm/Osterberg
HFD-550/PM/Gorski
HFD-550/Carreras
HFD-550/SMO/Chambers
HFD-550/Acting Div Director/Bull

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/s/

Lucious Lim
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MEDICAL OFFICER

Wiley Chambers
12/18/01 01:33:51 PM
MEDICAL OFFICER

Medical Officer's Review of NDA 20-490/SE5-007,
NDA 20-613/SE5-018, and NDA 21-262/SE5-006
Pediatric Supplement

NDA 20-490/SE5-007,
NDA 20-613/SE5-018,
NDA 21-262/SE5-006
Medical Officer's Review #2

Submission Dates: November 19, 2001
December 11, 2001
December 13, 2001
December 17, 2001
Review Completed: December 17, 2001

Trademark: ALPHAGAN® 0.5%, ALPHAGAN® 0.2%, and ALPHAGAN® P 0.15%

Generic Name: Brimonidine tartrate ophthalmic solutions 0.5%, 0.2%, and 0.15%

Sponsor: Allergan, Inc.
2525 Dupont Drive
P.O. Box 19534
Irvine, CA 92623-9534
(800) 347-4500

Pharmacologic Category: Alpha-2 adrenergic agonist

Indications: Reduction of intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension (NDA 20-613 & NDA 21-262)

Prevention of post-operative IOP elevation in patients undergoing argon laser trabeculoplasty (ALT) (NDA 20-490)

Dosage Form and Route of Administration: Ophthalmic solution for topical ocular administration

Submitted:

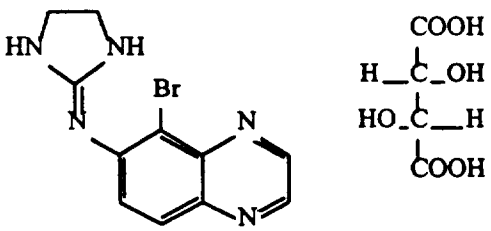
Submitted are proposed labels for NDA 20-490/SE5-007, NDA 21-613/SE5-018, and NDA 21-262/SE5-006.

ALPHAGAN®
(brimonidine tartrate ophthalmic solution) 0.5%

Sterile

DESCRIPTION

ALPHAGAN® (brimonidine tartrate ophthalmic solution) 0.5% is a relatively selective alpha-2 adrenergic agonist for ophthalmic use. The chemical name of brimonidine tartrate is 5-bromo-6-(2-imidazolidinylideneamino) quinoxaline L-tartrate. It has a molecular weight of 442.24 as the tartrate salt and is water soluble (34 mg/mL) pH 6.5. The structural formula is:



Formula: $C_{11}H_{10}BrN_5 \cdot C_4H_6O_6$

CAS Number: 59803-98-4

In solution, **ALPHAGAN®** (brimonidine tartrate ophthalmic solution) 0.5% has a clear, greenish-yellow color. It has a pH of 5.6 - 6.6.

Each mL of **ALPHAGAN®** contains:
Active ingredient: brimonidine tartrate 0.5% (5 mg/mL).
Preservative: benzalkonium chloride (0.05 mg).
Inactives: citric acid; polyvinyl alcohol; sodium chloride; sodium citrate; and purified water. Hydrochloric acid and/or sodium hydroxide may be added to adjust pH.

CLINICAL PHARMACOLOGY
Mechanism of action:

ALPHAGAN® is an alpha adrenergic receptor agonist. It has a peak ocular hypotensive effect occurring at two hours post-dosing.

Fluorophotometric studies in animals and humans suggest that brimonidine tartrate has a dual mechanism of action by reducing aqueous humor production and increasing uveoscleral outflow.

Pharmacokinetics:
After ocular administration of a 0.5% solution, plasma concentrations peaked within 1 to 4 hours and declined with a systemic half-life of approximately 3 hours. In humans, systemic metabolism of brimonidine is extensive. It is metabolized primarily by the liver. Urinary excretion is the major route of elimination of the drug and its metabolites. Approximately 87% of an orally-administered radioactive dose was eliminated within 120 hours, with 74% found in the urine.

Clinical Studies
Acute elevations in intraocular pressure (IOP) are a potentially serious complication of argon laser trabeculoplasty (ALT). The etiology of the IOP rise is not well understood. Acute elevations in IOP in susceptible patients can result in further optic nerve damage and visual field loss.

In two controlled, multi-center studies, **ALPHAGAN®** 0.5% ophthalmic solution was significantly more effective in decreasing the incidence of post-operative IOP elevations (increases of ≥10 mm Hg or more) than was the vehicle at one, two and three hours post-argon laser trabeculoplasty. An overall incidence of 1% of eyes treated with ALPHAGAN® ophthalmic solution had IOP elevations compared with an incidence of 23% of vehicle-treated eyes. An IOP increase of 5 mm Hg or greater post-ALT was reported in 6% of the ALPHAGAN® ophthalmic solution eyes compared with 40% of vehicle-treated eyes.

Incidence (%) of IOP Elevation ≥10 mmHg following Argon Laser Trabeculoplasty (360° of angle treated) when **ALPHAGAN®** ophthalmic solution 0.5% was used before and after ALT.

	Brimonidine	Placebo	P-Value
Study 1	1/62 (2%)	14/60 (23%)	>0.05
Study 2	1/60 (0%)	13/56 (23%)	<0.05

INDICATIONS AND USAGE
ALPHAGAN® 0.5% is indicated for the prevention of post-operative IOP elevations in patients undergoing argon laser trabeculoplasty (ALT).

CONTRAINDICATIONS
ALPHAGAN® is contraindicated in patients with hypersensitivity to brimonidine tartrate or any component of this medication. It is also contraindicated in patients receiving monoamine oxidase (MAO) inhibitor therapy.

PRECAUTIONS
General:

Although **ALPHAGAN®** had minimal effect on blood pressure of patients in clinical studies, caution should be exercised in treating patients with severe cardiovascular disease.

ALPHAGAN® has not been studied in patients with hepatic or renal impairment; caution should be used in treating such patients.

ALPHAGAN® should be used with caution in patients with depression, cerebral or coronary insufficiency, Raynaud's phenomenon, orthostatic hypotension or thromboangiitis obliterans.

Information for Patients:
The preservative in **ALPHAGAN®**, benzalkonium chloride, may be absorbed by soft contact lenses. Patients wearing soft contact lenses should be instructed to wait at least 15 minutes after instilling **ALPHAGAN®** to insert soft contact lenses.

As with other drugs of this class, **ALPHAGAN®** may cause fatigue and/or drowsiness in some patients. On the day of surgery, patients should be cautioned of the potential for a decrease in mental alertness.

Do not touch the tip of the unit-dose container to the eye or any other surface.

Drug Interactions:
Although specific drug interaction studies have not been conducted with **ALPHAGAN®**, the possibility of an additive or potentiating effect with CNS depressants (alcohol, barbiturates, opiates, sedatives, or anesthetics) should be considered. Alpha-agonists, as a class, may reduce pulse and blood pressure. Caution in using concomitant drugs such as beta blockers (ophthalmic and systemic), antihypertensives and/or cardiac glycosides is advised.

Tricyclic antidepressants have been reported to blunt the hypotensive effect of systemic clonidine. It is not known whether the concurrent use of these agents with **ALPHAGAN®** in humans can lead to resulting interference with the IOP lowering effect. No data on the level of circulating catecholamines after **ALPHAGAN®** instillation are available. Caution, however, is advised in patients taking tricyclic antidepressants which can affect the metabolism and uptake of circulating amines.

Carcinogenesis, mutagenesis, impairment of fertility:
No compound-related carcinogenic effects were observed in either mice or rats following a 21month and 24-month study, respectively. In these studies, dietary administration of brimonidine tartrate at doses up to 2.5 mg/kg/day in mice and 1.0 mg/kg/day in rats achieved ~77 and 118 times, respectively, the plasma drug concentration estimated in humans treated with one drop **ALPHAGAN®** into both eyes 3 times per day.

Brimonidine tartrate was not mutagenic or cytogenic in a series of *in vitro* and *in vivo* studies including the Ames test, chromosomal aberation assay in Chinese Hamster Ovary

(CHO) cells, a host-mediated assay and cytogenic studies in mice, and dominant lethal assay.

Reproductive studies performed in rats with oral doses of 0.66 mg base/kg revealed no evidence of impaired fertility due to **ALPHAGAN®**.

Pregnancy: Teratogenic Effects: Pregnancy Category B
Reproductive studies performed in rats with oral doses of 0.66 mg base/kg revealed no evidence of harm to the fetus due to **ALPHAGAN®**. Dosing at this level produced 100 times the plasma drug concentration level seen in humans following multiple ophthalmic doses. There are no adequate and well-controlled studies in pregnant women.

In animal studies, brimonidine crossed the placenta and entered into the fetal circulation to a limited extent. **ALPHAGAN®** should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus.

Nursing Mothers:
It is not known whether this drug is excreted in human milk; in animal studies brimonidine tartrate was excreted in breast milk. 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.

Pediatric Use:
In a well-controlled clinical study conducted in pediatric glaucoma patients (ages 2 to 7 years) the most commonly observed adverse events with brimonidine tartrate ophthalmic solution 0.2% dosed three times daily were somnolence (50% - 83% in patients ages 2 to 6 years) and decreased alertness. In pediatric patients 7 years of age or older (>20kg), 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 **ALPHAGAN®** have not been studied in pediatric patients below the age of 2 years. **ALPHAGAN®** is not recommended for use in pediatric patients under the age of 2 years.

Geriatric Use:
No overall differences in safety or effectiveness have been observed between elderly and other adult patients.

ADVERSE REACTIONS

The most common adverse events reported in association with the use of **ALPHAGAN®** 0.5% in conjunction with ALT was transient conjunctival blanching in 50% of patients and upper lid retraction in 30% of patients.

The following adverse reactions were reported in 1% to 4% of the patients: corneal edema, dizziness, drowsiness/tiredness, and ocular irritation (encompassing discomfort, foreign body sensation, and ocular pain.

The following were reported in 1% or less of patients: browache, dry mouth, nausea.

OVERDOSAGE

No information is available on overdosage in humans. Treatment of an oral overdose includes supportive and symptomatic therapy; a patent airway should be maintained.

DOSAGE AND ADMINISTRATION

Instill 1 drop of **ALPHAGAN®** in the operative eye 30-45 minutes before ALT surgery and immediately following ALT surgery.

HOW SUPPLIED

ALPHAGAN® (brimonidine tartrate ophthalmic solution) 0.5% is supplied sterile in unit dose vials of LDPE plastic containing 0.4 mL each and packaged in cartons containing 24 vials; NDC 0023-XXXX-XX

NOTE: Store between 15°-25° C (59-77° F). Properly dispose of unit-dose vial after each single patient use.

Rx only

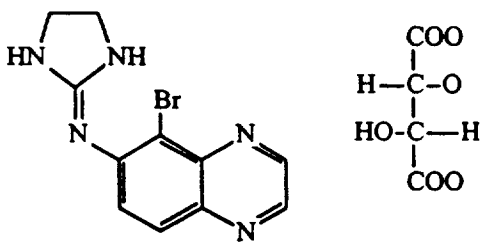
US Patent 6,194,415
Revised December 2001
7831X

ALPHAGAN®
(brimonidine tartrate ophthalmic solution) 0.2%

Sterile

DESCRIPTION

ALPHAGAN® (brimonidine tartrate ophthalmic solution) 0.5% is a relatively selective alpha-2 adrenergic agonist for ophthalmic use. The chemical name of brimonidine tartrate is 5-bromo-6-(2-imidazolidinylideneamino) quinoxaline L-tartrate. It has a molecular weight of 442.24 as the tartrate salt and is water soluble (34 mg/mL) at pH 6.5. The structural formula is:



Formula: $C_{11}H_{10}BrN_5 \cdot C_4H_6O_6$

CAS Number 59803-98-4

In solution, **ALPHAGAN®** (brimonidine tartrate ophthalmic solution) 0.2% has a clear, greenish-yellow color. It has an osmolality of 280 – 330 mOsml/kg and a pH of 5.6 - 6.6.

Each mL of **ALPHAGAN®** contains:
Active ingredient: brimonidine tartrate: 0.2% (2 mg/mL).
Preservative: benzalkonium chloride (0.05 mg).
Inactives: citric acid; polyvinyl alcohol; sodium chloride; sodium citrate; and purified water. Hydrochloric acid and/or sodium hydroxide may be added to adjust pH.

CLINICAL PHARMACOLOGY

Mechanism of action:
ALPHAGAN® is an alpha adrenergic receptor agonist. It has a peak ocular hypotensive effect occurring at two hours post-dosing. Fluorophotometric studies in animals and humans suggest that brimonidine tartrate has a dual mechanism of action by reducing aqueous humor production and increasing uveoscleral outflow.

Pharmacokinetics:
After ocular administration of a 0.2% solution, plasma concentrations peaked within 1 to 4 hours and declined with a systemic half-life of approximately 3 hours. In humans, systemic metabolism of brimonidine is extensive. It is metabolized primarily by the liver. Urinary excretion is the major route of elimination of the drug and its metabolites. Approximately 87% of an orally-administered radioactive dose was eliminated within 120 hours, with 74% found in the urine.

Clinical Evaluations:
Elevated IOP presents a major risk factor in glaucomatous field loss. The higher the level of IOP, the greater the likelihood of optic nerve damage and visual field loss. Brimonidine tartrate has the action of lowering intraocular pressure with minimal effect on cardiovascular and pulmonary parameters.

In comparative clinical studies with timolol 0.5%, lasting up to one year, the IOP lowering effect of **ALPHAGAN®** was approximately 4-6 mm Hg compared with approximately 6 mm Hg for timolol. In these studies, both patient groups were dosed BID; however, due to the duration of action of **ALPHAGAN®**, it is recommended that **ALPHAGAN®** be dosed TID. Eight percent of subjects were discontinued from studies due to inadequately controlled intraocular pressure, which in 30% of these patients occurred during the first month of therapy. Approximately 20% were discontinued due to adverse experiences.

INDICATIONS AND USAGE
ALPHAGAN® is indicated for lowering intraocular pressure in patients with open-angle glaucoma or ocular hypertension. The IOP lowering efficacy of **ALPHAGAN®** Ophthalmic Solution diminishes over time in some patients. This loss of effect appears with a variable time of onset in each patient and should be closely monitored.

CONTRAINDICATIONS
ALPHAGAN® is contraindicated in patients with hypersensitivity to brimonidine tartrate or any component of this medication. It is also contraindicated in patients receiving monoamine oxidase (MAO) inhibitor therapy.

PRECAUTIONS
General:
Although **ALPHAGAN®** had minimal effect on blood pressure of patients in clinical studies, caution should be exercised in treating patients with severe cardiovascular disease.

ALPHAGAN® has not been studied in patients with hepatic or renal impairment; caution should be used in treating such patients.

ALPHAGAN® should be used with caution in patients with depression, cerebral or coronary insufficiency, Raynaud's phenomenon, orthostatic hypotension or thromboangiitis obliterans.

During the studies there was a loss of effect in some patients. The IOP-lowering efficacy observed with **ALPHAGAN®** Ophthalmic Solution during the first month of therapy may not always reflect the long-term level of IOP reduction. Patients prescribed IOP-lowering medication should be routinely monitored for IOP.

Information for Patients:
The preservative in **ALPHAGAN®**, benzalkonium chloride, may be absorbed by soft contact lenses. Patients wearing soft contact lenses should be instructed to wait at least 15 minutes after instilling **ALPHAGAN®** to insert soft contact lenses.

As with other drugs in this class, **ALPHAGAN®** may cause fatigue and/or drowsiness in some patients. Patients who engage in hazardous activities should be cautioned of the potential for a decrease in mental alertness.

Drug Interactions:
Although specific drug interaction studies have not been conducted with **ALPHAGAN®**, the possibility of an additive or potentiating effect with CNS depressants (alcohol, barbiturates, opiates, sedatives, or anesthetics) should be considered. Alpha-agonists, as a class, may reduce pulse and blood pressure. Caution in using concomitant drugs such as beta-blockers (ophthalmic and systemic), antihypertensives and/or cardiac glycosides is advised.

Tricyclic antidepressants have been reported to blunt the hypotensive effect of systemic clonidine. It is not known whether the concurrent use of these agents with **ALPHAGAN®** in humans can lead to resulting interference with the IOP lowering effect. No data on the level of circulating catecholamines after **ALPHAGAN®** are available. Caution, however, is advised in patients taking tricyclic antidepressants which can affect the metabolism and uptake of circulating amines.

Carcinogenesis, mutagenesis, impairment of fertility:
No compound-related carcinogenic effects were observed in either mice or rats following a 21-month and 24-month study, respectively. In these studies, dietary administration of brimonidine tartrate at doses up to 2.5 mg/kg/day in mice and 1.0 mg/kg/day in rats achieved ~77 and 118 times, respectively, the plasma drug concentration estimated in humans treated with one drop **ALPHAGAN®** into both eyes 3 times per day.

Brimonidine tartrate was not mutagenic or cytogenic in a series of *in vitro* and *in vivo* studies including the Ames test, chromosomal aberation assay in Chinese Hamster Ovary (CHO) cells, a host-mediated assay and cytogenic studies in mice, and dominant lethal assay.

Reproductive studies performed in rats with oral doses of 0.66 mg base/kg revealed no evidence of harm to the fetus due to **ALPHAGAN®**.

Pregnancy: Teratogenic Effects: Pregnancy Category B

Reproductive studies performed in rats with oral doses of 0.66 mg base/kg revealed no evidence of harm to the fetus due to **ALPHAGAN®**. Dosing at this level produced 100 times the plasma drug concentration level seen in humans following multiple ophthalmic doses.

There are no adequate and well-controlled studies in pregnant women. In animal studies, brimonidine crossed the placenta and entered into the fetal circulation to a limited extent. **ALPHAGAN®** should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus.

Nursing Mothers:
It is not known whether this drug is excreted in human milk; in animal studies brimonidine tartrate was excreted in breast milk. 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.

Pediatric Use:
In a well-controlled clinical study conducted in pediatric glaucoma patients (ages 2 to 7 years) the most commonly observed adverse events with brimonidine tartrate ophthalmic solution 0.2% dosed three times daily were somnolence (50% - 83% in patients ages 2 to 6 years) and decreased alertness. In pediatric patients 7 years of age or older (>20kg), somnolence appears to occur less frequently (25%). The most commonly observed adverse event was somnolence. Approximately 16% of patients on brimonidine tartrate ophthalmic solution discontinued from the study due to somnolence.

The safety and effectiveness of **ALPHAGAN®** have not been studied in pediatric patients below the age of 2 years. **ALPHAGAN®** is not recommended for use in pediatric patients under the age of 2 years. (Also refer to Adverse Reactions section.)

Geriatric Use:
No overall differences in safety or effectiveness have been observed between elderly and other adult patients.

ADVERSE REACTIONS

Adverse events occurring in approximately 10-30% of the subjects, in descending order of incidence, included oral dryness, ocular hyperemia, burning and stinging, headache, blurring, foreign body sensation, fatigue/drowsiness, conjunctival follicles, ocular allergic reactions, and ocular pruritus.

Events occurring in approximately 3-9% of the subjects, in descending order included corneal staining/erosion, photophobia, eyelid erythema, ocular ache/pain, ocular dryness, tearing, upper respiratory symptoms, eyelid edema, conjunctival edema, dizziness, blepharitis, ocular irritation, gastrointestinal symptoms, asthenia, conjunctival blanching, abnormal vision and muscular pain.

The following adverse reactions were reported in less than 3% of the patients: lid crusting, conjunctival hemorrhage, abnormal taste, insomnia, conjunctival discharge, depression, hypertension, anxiety, palpitations/arrhythmias, nasal dryness and syncope. The following events have been identified during post-marketing use of **ALPHAGAN®** in clinical practice. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. The events, which have been chosen for inclusion due to either their seriousness, frequency of reporting, possible causal connection to **ALPHAGAN®**, or a combination of these factors, include: bradycardia; hypotension; iritis; miosis; skin reactions (including erythema, eyelid pruritis, rash, and vasodilation); and tachycardia. Apnea, bradycardia, hypotension, hypothermia, hypotonia, and somnolence have been reported in infants receiving **ALPHAGAN®**.

OVERDOSAGE

No information is available on overdosage in humans. Treatment of an oral overdose includes supportive and symptomatic therapy; a patent airway should be maintained.

DOSAGE AND ADMINISTRATION

The recommended dose is one drop of **ALPHAGAN®** in the affected eye(s) three times daily, approximately 8 hours apart.

ALPHAGAN® may be used concomitantly with other topical ophthalmic drug products to lower intraocular pressure. If more than one topical ophthalmic product is being used, the products should be administered at least 5 minutes apart.

HOW SUPPLIED

ALPHAGAN®(brimonidine tartrate ophthalmic solution) 0.2% is supplied sterile in white opaque LPDE plastic bottles with tips with purple high impact polystyrene (HIPS) caps as follows:

5 mL in 10 mL bottle	NDC 0023-8665-05
10 mL in 10 mL bottle	NDC 0023-8665-10
15 mL in 15 mL bottle	NDC 0023-8665-15

NOTE: Store between 15°-25° C (59-77° F).

Rx only

ALLERGAN®

Irvine, CA 92612

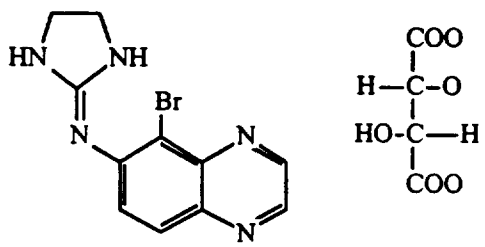
US Patent 6,194,415
Revised December 2001
7831X

ALPHAGAN® P
(brimonidine tartrate ophthalmic solution) 0.15%

Sterile

DESCRIPTION

ALPHAGAN® P (brimonidine tartrate ophthalmic solution) 0.15% is a relatively selective alpha-2 adrenergic agonist for ophthalmic use. The chemical name of brimonidine tartrate is 5-bromo-6-(2-imidazolidinylideneamino) quinoxaline L-tartrate. It is an off-white to pale yellow powder. It has a molecular weight of 442.24 as the tartrate salt, and is both soluble in water (1.5 mg/mL) and in the product vehicle (3.0 mg/mL) at pH 7.2. The structural formula is:



Formula: $C_{11}H_{10}BrN_5 \cdot C_4H_6O_6$

CAS Number: 59803-98-4

In solution, **ALPHAGAN® P** (brimonidine tartrate ophthalmic solution) 0.15% has a clear, greenish-yellow color. It has an osmolality of 250-350 mOsmol/kg and a pH of 6.6-7.4.

Each mL of **ALPHAGAN® P** contains:
Active ingredient: brimonidine tartrate 0.15% (1.5 mg/mL)
Preservative: Purite® 0.005% (0.05mg/mL)
Inactives: boric acid; calcium chloride; magnesium chloride; potassium chloride; purified water; sodium borate; sodium carboxymethylcellulose; sodium chloride; with hydrochloric acid and/or sodium hydroxide to adjust pH.

CLINICAL PHARMACOLOGY

Mechanism of action:
ALPHAGAN® P is an alpha adrenergic receptor agonist. It has a peak ocular hypotensive effect occurring at two hours post-dosing. Fluorophotometric studies in

animals and humans suggest that brimonidine tartrate has a dual mechanism of action by reducing aqueous humor production and increasing uveoscleral outflow.

Pharmacokinetics:
After ocular administration of either a 0.1% or 0.2% solution, plasma concentrations peaked within 0.5 to 2.5 hours and declined with a systemic half-life of approximately 2 hours. In humans, systemic metabolism of brimonidine is extensive. It is metabolized primarily by the liver. Urinary excretion is the major route of elimination of the drug and its metabolites. Approximately 87% of an orally-administered radioactive dose was eliminated within 120 hours, with 74% found in the urine.

Clinical Evaluations:
Elevated IOP presents a major risk factor in glaucomatous field loss. The higher the level of IOP, the greater the likelihood of optic nerve damage and visual field loss. Brimonidine tartrate has the action of lowering intraocular pressure with minimal effect on cardiovascular and pulmonary parameters.

Two clinical studies were conducted to evaluate the safety, efficacy, and acceptability of **ALPHAGAN® P** (brimonidine tartrate ophthalmic solution) 0.15% compared with **ALPHAGAN®** administered three-times-daily in patients with open-angle glaucoma or ocular hypertension. Those results indicated that **ALPHAGAN® P** (brimonidine tartrate ophthalmic solution) 0.15% is comparable in IOP lowering effect to **ALPHAGAN®** (brimonidine tartrate ophthalmic solution) 0.2%, and effectively lowers IOP in patients with open-angle glaucoma or ocular hypertension by approximately 2-5 mmHg.

INDICATIONS AND USAGE
ALPHAGAN® P is indicated for the lowering of intraocular pressure in patients with open-angle glaucoma or ocular hypertension.

CONTRAINDICATIONS
ALPHAGAN® P is contraindicated in patients with hypersensitivity to brimonidine tartrate or any component of this medication. It is also contraindicated in patients receiving monoamine oxidase (MAO) inhibitor therapy.

PRECAUTIONS
General:
Although **ALPHAGAN® P** had minimal effect on the blood pressure of patients in clinical studies, caution should be exercised in treating patients with severe cardiovascular disease.

ALPHAGAN® P has not been studied in patients with hepatic or renal impairment; caution should be used in treating such patients.

ALPHAGAN® P should be used with caution in patients with depression, cerebral or coronary insufficiency, Raynaud's phenomenon, orthostatic hypotension, or thromboangitis obliterans. Patients prescribed IOP-lowering medication should be routinely monitored for IOP.

Information for Patients:
As with other drugs in this class, **ALPHAGAN® P** may cause fatigue and /or drowsiness in some patients. Patients who engage in hazardous activities should be cautioned of the potential for a decrease in mental alertness.

Drug Interactions:
Although specific drug interaction studies have not been conducted with **ALPHAGAN® P**, the possibility of an additive or potentiating effect with CNS depressants (alcohol, barbiturates, opiates, sedatives, or anesthetics) should be considered. Alpha-agonists, as a class, may reduce pulse and blood pressure. Caution in using concomitant drugs such as beta-blockers (ophthalmic and systemic), anti-hypertensives and/or cardiac glycosides is advised.

Tricyclic antidepressants have been reported to blunt the hypotensive effect of systemic clonidine. It is not known whether the concurrent use of these agents with **ALPHAGAN® P** in humans can lead to resulting interference with the IOP lowering effect. No data on the level of circulating catecholamines after **ALPHAGAN® P** administration are available. Caution, however, is advised in patients taking tricyclic antidepressants which can affect the metabolism and uptake of circulating amines.

Carcinogenesis, Mutagenesis, and Impairment of Fertility:
No compound-related carcinogenic effects were observed in either mice or rats following a 21-month and 24-month study, respectively. In these studies, dietary administration of brimonidine tartrate at doses up to 2.5 mg/kg/day in mice and 1.0 mg/kg/day in rats achieved 86 and 55 times, respectively, the plasma drug concentration estimated in humans treated with one drop of **ALPHAGAN® P** into both eyes 3 times per day.

Brimonidine tartrate was not mutagenic or cytogenic in a series of *in vitro* and *in vivo* studies including the Ames test, chromosomal aberration assay in Chinese Hamster Ovary (CHO) cells, a host-mediated assay and cytogenic studies in mice, and dominant lethal assay.

Reproductive studies performed in rats with oral doses of 0.66 mg base/kg revealed no evidence of impaired fertility due to **ALPHAGAN® P.**

Pregnancy: Teratogenic effects: Pregnancy Category B
Reproductive studies performed in rats with oral doses of 0.66 mg base/kg revealed no evidence of harm to the fetus due to **ALPHAGAN® P.** Dosing at this level produced an exposure that is 189 times higher than the exposure seen in humans following multiple ophthalmic doses.

There are no adequate and well-controlled studies in pregnant women. In animal studies, brimonidine crossed the placenta and entered into the fetal circulation to a limited extent. **ALPHAGAN® P** should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus.

Nursing Mothers:
It is not known whether this drug is excreted in human milk; in animal studies brimonidine tartrate was excreted in breast milk. 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.

Pediatric Use:
In a well-controlled clinical study conducted in pediatric glaucoma patients (ages 2 to 7 years) the most commonly observed adverse events with brimonidine tartrate ophthalmic solution 0.2% dosed three times a day were somnolence (50% - 83% in patients ages 2 to 6 years) and decreased alertness. In pediatric patients 7 years of age or older (20kg), 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 ophthalmic solution have not been studied in pediatric patients below the age of 2 years. Brimonidine tartrate ophthalmic solution is not recommended for use in pediatric patients under the age of 2 years. (Also refer to Adverse Reactions section.)

Geriatric Use:
No overall differences in safety or effectiveness have been observed between elderly and other adult patients.

ADVERSE REACTIONS
Adverse events occurring in approximately 10-20% of the subjects included: allergic conjunctivitis, conjunctival hyperemia, and eye pruritis.

Adverse events occurring in approximately 5-9% of the subjects included: burning sensation, conjunctival foliculosis, hypertension, oral dryness, and visual disturbance.

Events occurring in approximately 1-4% of subjects included: allergic reaction, asthenia, blepharitis, bronchitis, conjunctival edema, conjunctival hemorrhage, conjunctivitis, cough, dizziness, dyspepsia, dyspnea, epiphora, eye discharge, eye dryness, eye irritation, eye pain, eyelid edema, eyelid erythema, flu syndrome, follicular conjunctivitis, foreign body sensation, headache, pharyngitis, photophobia, rash, rhinitis, sinus infection, sinusitis, stinging, superficial punctate keratopathy, visual field defect, vitreous floaters, and worsened visual acuity.

The following events were reported in less than 1% of subjects: corneal erosion, insomnia, nasal dryness, somnolence, and taste perversion.

The following events have been identified during post-marketing use of **ALPHAGAN®** in clinical practice. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. The events, which have been chosen for inclusion due to either their seriousness, frequency of reporting, possible causal connection to **ALPHAGAN®**, or a combination of these factors, include: bradycardia; hypotension; iritis; miosis; skin reactions (including erythema, eyelid pruritis, rash, and

vasodilation); and tachycardia. Apnea, bradycardia, hypotension, hypothermia, hypotonia, and somnolence have been reported in infants receiving **ALPHAGAN®**.

OVERDOSAGE

No information is available on overdosage in humans. Treatment of an oral overdose includes supportive and symptomatic therapy; a patent airway should be maintained.

DOSAGE AND ADMINISTRATION

The recommended dose is one drop of **ALPHAGAN® P** in the affected eye(s) three times daily, approximately 8 hours apart.

ALPHAGAN® P may be used concomitantly with other topical ophthalmic drug products to lower intraocular pressure. If more than one topical ophthalmic product is being used, the products should be administered at least 5 minutes apart.

HOW SUPPLIED

ALPHAGAN® P (brimonidine tartrate ophthalmic solution) 0.15% is supplied sterile in opaque teal LDPE plastic bottles and tips with purple high impact polystyrene (HIPS) caps as follows:

5 mL in 10 mL bottle	NDC 0023-9177-05
10 mL in 10 mL bottle	NDC 0023-9177-10
15 mL in 15 mL bottle	NDC 0023-9177-15

NOTE: Store between 15°-25° C (59-77°F).

Rx Only

ALLERGAN®

US Patent 5,424,078; 5,736,165
Revised December 2001
7831X

Reviewer's Comments:

Acceptable.

Recommended Regulatory Action:

The above proposed labels are recommended for approval.

Lucious Lim, M.D., M.P.H.
Medical Officer

NDA 20-490, NDA 20-613, and NDA 21-262
HFD-550/Div Files
HFD-550/CSO/Gorski
HFD-550/Biopharm/Bashaw
HFD-550/Biostats/Lin
HFD-550/Chem/Rodriguez
HFD-550/Pharm/Osterberg
HFD-550/MO/Lim
HFD-550/SMO/Chambers
HFD-550/Div Director/Simon

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

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12/20/01 02:49:21 PM
MEDICAL OFFICER

Wiley Chambers
12/20/01 04:17:07 PM
MEDICAL OFFICER