CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-770

MEDICAL REVIEW

Medical Officer's Review of NDA 21-770
Labeling Review # 3

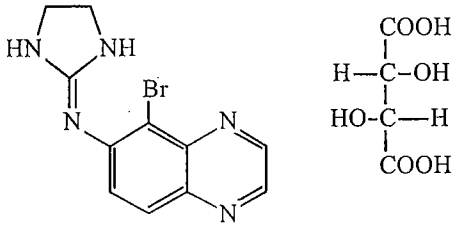
NDA 21-770
Medical Officer's Review

Submission: 8/03/05
Submission: 8/18/05
Review Completed: 8/18/05

Proposed Tradename: Alphagan P

Established Name: brimonidine tartrate ophthalmic solution, 0.1%

Chemical Structure:



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

Sponsor: Allergan, Inc.
2525 Dupont Drive
P.O. Box 19534
Irvine, CA 92623-9534

Pharmacologic Category: Alpha 2-agonist

Proposed Indication: Reduction of intraocular pressure (IOP)

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

Submitted:

The following comments are from the DMETS review signed August 12, 2005:

A. GENERAL COMMENTS

1. We note that the preservative for this product bears the tradename "Purite®". We ask that you define Purite® in terms of its ingredients where it appears throughout your labels and labeling.

Reviewer's comments:

Purite® is a "stabilized oxychloro complex." Defining Purite® within the labeling will provide no additional beneficial information.

2. DMETS is aware of postmarketing reports of inadvertent oral administration of Alphagan resulting in hospitalization of pediatric patients. DMETS recommends the addition of a prominent statement on container labels and carton labeling of "Alphagan" products that these product are for use only in the eye. Alternatively (or additionally), DMETS recommends that an eye pictorial appear on those labels and labeling.

Reviewer's comments:

The cases referenced are children who accidentally ingested the medication not cases in which drug was mis-administered; it is unlikely that an eye pictorial or label statement would prevent accidental ingestion.

3. DMETS recommends that the statement, "New Product Strength" appears on product labels and labeling for a period of time not to exceed six months.

Reviewer's comments:

The proposed drug product is bioequivalent to the currently marketed product. There is no safety or efficacy issue related to substitution of these products.

4. When preparing product labeling, please ensure that the expression of strength is well differentiated from the expression of strength of the existing Alphagan P product. DMETS recommends the use of contrasting colors, boxing, or some other means to differentiate the product strengths.

Reviewer's comments:

The boxes for these products do differ in color. The Alphagan P 0.15% box top is in purple, while the Alphagan P 0.1% box top is in green. Even if one drug was inadvertently substituted for the other, these drugs are bioequivalent and have the same safety and efficacy profile.

5. According to the Division's Project Manager, the sponsor has proposed a separate package insert for the lower strength product. DMETS does not

recommend two separate package inserts for the two different strengths as this may cause confusion and error. For example, practitioners may not be aware of the two different strengths if only one strength is listed and/or they may think that the products are not indicated or dosed similarly. Traditionally, a combined package insert is used for different strengths of the same active ingredient.

Reviewer's comments:

A combined package insert will be used for both products (Alphagan P 0.15% and Alphagan P 0.1%).

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✓ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Medical- 1

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/s/

Martin Nevitt
8/18/2005 01:22:11 PM
MEDICAL OFFICER

William Boyd
8/18/2005 01:45:11 PM
MEDICAL OFFICER

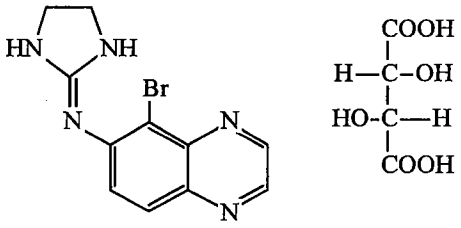
Wiley Chambers
8/18/2005 03:15:33 PM
MEDICAL OFFICER

Lillian Gavrilovich
8/19/2005 09:00:15 AM
MEDICAL OFFICER
Sigbning for Dr. Soreth.

LABELING REVIEW

Application Type	NDA 21-770 Label Review Class 1 Resubmission
Letter Date	6/27/05
PDUFA Goal Date	8/28/05
Reviewer Name	Martin P. Nevitt, M.D., M.P.H.
Review Completion Date	7/18/05
Established Name	Brimonidine Tartrate Ophthalmic Solution, 0.1%
(Proposed) Trade Name	Alphagan P
Therapeutic Class	Alpha 2 -agonist
Applicant	Allergan, Inc. 2525 Dupont Drive P.O. Box 19534 Irvine, CA 92623-9534 714-246-4500 FAX: 714-246-4272 Lewis Gryziewicz 714-246-6088
Priority Designation	S

Structure $C_{11}H_{10}BrN_5 \cdot C_4H_6O_6$



Dosing Regimen One drop in the affected eye three times daily

Indication Reduction of intraocular pressure (IOP)

Intended Population Patients 2 years or older with open angle glaucoma or ocular hypertension

Submitted:

The applicant has submitted the following labeling based on the April 1, 2005, approvable letter.

Reviewer's comments:

Reviewer's deletions are noted by a and additions by an underline within this review.

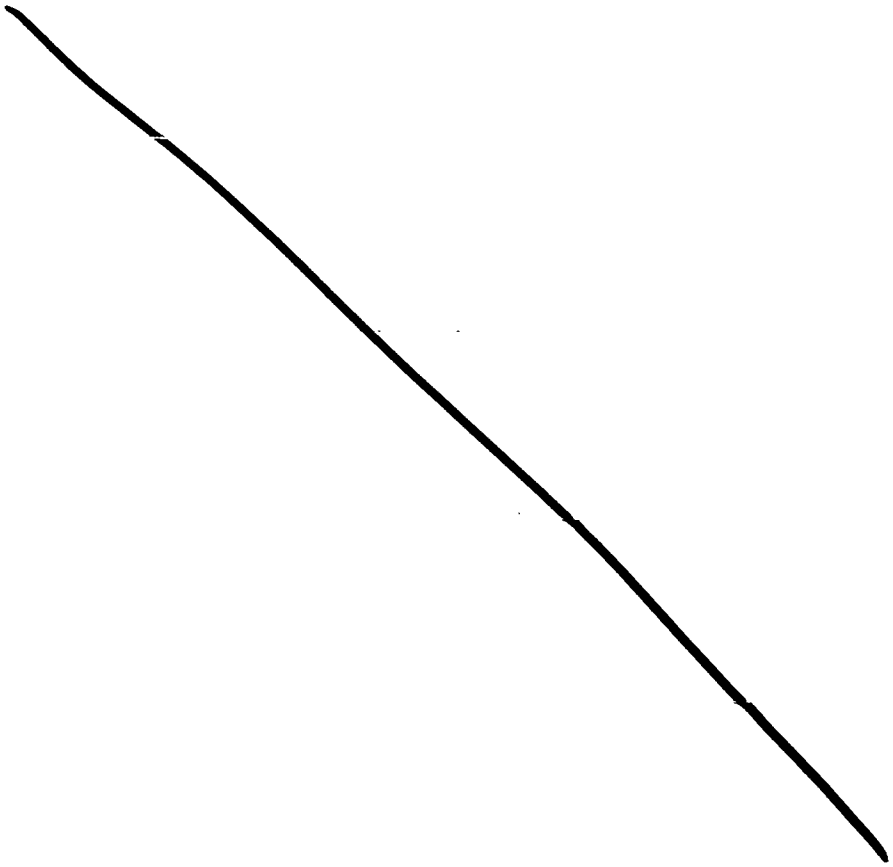
Allergan, Inc.

ALPHAGAN P

(brimonidine tartrate ophthalmic solution) 0.1%

Sterile

DESCRIPTION



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✓ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Medical- 2

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/s/

Martin Nevitt
7/19/05 02:00:16 PM
MEDICAL OFFICER

William Boyd
7/19/05 02:03:45 PM
MEDICAL OFFICER

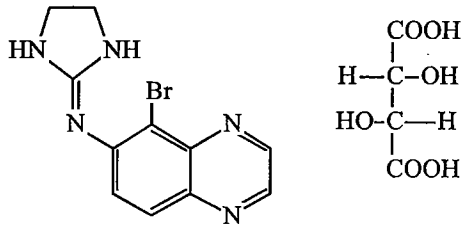
Wiley Chambers
7/19/05 05:19:55 PM
MEDICAL OFFICER

Janice Soreth
8/10/05 09:45:42 AM
MEDICAL OFFICER

LABELING REVIEW

Application Type	NDA 21-770 Label Review 1 – March 28, 2005
PDUFA Goal Date	4/1/05
Reviewer Name	Martin P. Nevitt, M.D., M.P.H.
Review Completion Date	3/28/05
Established Name	Brimonidine Tartrate Ophthalmic Solution, 0.1%
(Proposed) Trade Name	Alphagan [redacted]
Therapeutic Class	Alpha 2 -agonist
Applicant	Allergan, Inc. 2525 Dupont Drive P.O. Box 19534 Irvine, CA 92623-9534 714-246-4500 FAX: 714-246-4272 Lewis Gryziewicz 714-246-6088
Priority Designation	S

Structure $C_{11}H_{10}BrN_5 \cdot C_4H_6O_6$



Dosing Regimen One drop in the affected eye three times daily

Indication Reduction of intraocular pressure (IOP)

Intended Population Patients 2 years or older with open angle glaucoma or ocular hypertension

The original labeling review (clean copy) has been updated to include the recommendations/suggestions from the pharm/tox review and from the chemistry team leader.

Reviewer's comments:
Reviewer's deletion's are noted by a and additions by an underline within this review.

Allergan, Inc.

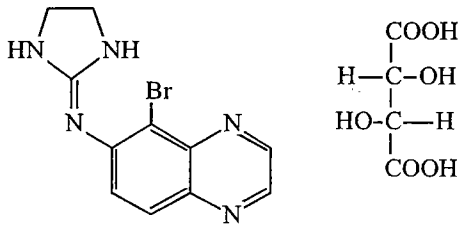
Alphagan [redacted]

(brimonidine tartrate ophthalmic solution) 0.1%

Sterile

DESCRIPTION

Alphagan LS™ (brimonidine tartrate ophthalmic solution) [redacted] 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 (0.6 mg/mL) and in the product vehicle (1.4 mg/mL) at pH 7.7. The structural formula is:



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

CAS Number: 70359-46-5

In solution, **Alphagan** [redacted] (brimonidine tartrate ophthalmic solution) [redacted] has a clear, greenish-yellow color. It has an osmolality of 250-320 mOsmol/kg and a pH of 7.4-8.0.

Each mL of **Alphagan** [redacted] contains:

Active ingredient: brimonidine tartrate 0.1% (1.0 mg/mL)

Inactives: sodium carboxymethylcellulose; sodium borate; boric acid; sodium chloride; potassium chloride; calcium chloride; magnesium chloride; (Purite® 0.005% (0.05 mg/ml) as a preservative) purified water; with hydrochloric acid and/or sodium hydroxide to adjust pH.

Reviewer's comments:
Per discussion with the chemistry team leader, preservative information has been included within the "Inactives" section.

Mechanism of action:

Alphagan [redacted] 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.

Reviewer's comments:

[redacted]

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.

A clinical study was conducted to evaluate the safety, efficacy, and acceptability of **Alphagan** [redacted] (brimonidine tartrate ophthalmic solution) [redacted] compared with **ALPHAGAN®** administered three-times-daily in patients with open-angle glaucoma or ocular hypertension.

Those results indicated that **Alphagan** [redacted] (brimonidine tartrate ophthalmic solution) [redacted] is equivalent 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- 6 mmHg.

INDICATIONS AND USAGE

Alphagan [redacted] is indicated for the lowering of intraocular pressure in patients with open-angle glaucoma or ocular hypertension.

CONTRAINDICATIONS

Alphagan [redacted] 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 brimonidine tartrate ophthalmic solution had minimal effect on the blood pressure of patients in clinical studies, caution should be exercised in treating patients with severe cardiovascular disease.

Alphagan [redacted] has not been studied in patients with hepatic or renal impairment; caution should be used in treating such patients.

Alphagan [redacted] should be used with caution in patients with depression, cerebral or coronary insufficiency, Raynaud's phenomenon, orthostatic hypotension, or thromboangiitis obliterans. Patients prescribed IOP-lowering medication should be routinely monitored for IOP.

Information for Patients:

As with other drugs in this class, Alphagan [redacted] 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 [redacted] 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 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 [redacted] in humans can lead to resulting interference with the IOP lowering effect. No data on the level of circulating catecholamines after Alphagan [redacted] 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 150 and 120 times, respectively, the plasma drug concentration (Cmax) estimated in humans treated with one drop of Alphagan [redacted] into both eyes 3 times per day.

Reviewer's comments:

The pharm/tox reviewer has recommended the changes listed within the Carcinogenesis section. The changes are acceptable and have been included within this updated label.

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.

Pregnancy: Teratogenic effects: Pregnancy Category B.
Reproductive studies performed in rats and rabbits with oral doses of 0.66 mg base/kg revealed no evidence of impaired fertility or harm to the fetus due to Alphagan [redacted] Dosing at this level produced an exposure in rats and rabbits that is 190 and 100 times higher, respectively, 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 [redacted] should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus.

Reviewer's comments:
The pharm/tox reviewer has recommended the changes listed within the Pregnancy section. The changes are acceptable and have been included within this updated label.

Nursing Mothers:
It is not known whether this drug is excreted in human milk; although 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 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 EVENTS

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 receiving brimonidine ophthalmic solution (0.1 – 0.2%) included: burning sensation, conjunctival folliculosis, hypertension, ocular allergic reaction, oral dryness, and visual disturbance.

Events occurring in approximately 1-4% of subjects receiving brimonidine ophthalmic solution (0.1 – 0.2%) included: allergic reaction, [redacted], asthenia, blepharitis, blepharoconjunctivitis, blurred vision, bronchitis, [redacted] conjunctival edema, conjunctival hemorrhage, conjunctivitis, cough, dizziness, [redacted] dyspepsia, dyspnea, epiphora, eye discharge, eye dryness, eye irritation, eye pain, eyelid edema, eyelid erythema, fatigue, flu syndrome, follicular conjunctivitis, foreign body sensation, gastrointestinal disorder, headache, hypercholesterolemia, hypotension, infection, insomnia, [redacted] keratitis, lid disorder, [redacted], pharyngitis, photophobia, rash, rhinitis, sinus infection, sinusitis, somnolence, stinging, superficial punctate keratopathy, tearing, visual field defect, vitreous detachment, vitreous disorder, vitreous floaters, and worsened visual acuity.

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

The following events have been identified during post-marketing use of brimonidine tartrate ophthalmic solutions 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 brimonidine tartrate ophthalmic solutions, or a combination of these factors, include: bradycardia; depression; keratoconjunctivitis sicca; iritis; miosis; nausea; skin reactions (including erythema, eyelid pruritis, rash, and vasodilation); and tachycardia. Apnea, bradycardia, hypotension, hypothermia, hypotonia, and somnolence have been reported in infants receiving brimonidine tartrate ophthalmic solutions.

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 [redacted] in the affected eye(s) three times daily, approximately 8 hours apart.

Alphagan [redacted] ophthalmic solution 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 [redacted] is supplied sterile in opaque teal LDPE plastic bottles and droppers with purple high impact polystyrene (HIPS) caps as follows:

Reviewer's comments:

Per discussion with the chemistry team leader, the How Supplied section has been revised.

5 mL in 10mL bottle	NDC XXXX-XXXX-XX
10 mL in 10 mL bottle	NDC XXXX-XXXX-XX
15 mL in 15 mL bottle	NDC XXXX-XXXX-XX

NOTE: Store at 15°-25° C (59-77°F).

Rx Only

Recommendation:

It is recommended that NDA 21-770 be approved with the changes to the label noted in this review.

Martin P. Nevitt, M.D., M.P.H.
Medical Officer

Cc:
NDA 21-770
HFD-550/PM/Puglisi
HFD-550/TL/Ng
HFD-550/TL/Yang
HFD-550/MO/Nevitt
HFD-550/TL/Boyd
HFD-550/DepDir/Chambers

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/s/

Martin Nevitt
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William Boyd
3/29/05 02:33:02 PM
MEDICAL OFFICER

Wiley Chambers
3/29/05 03:30:18 PM
MEDICAL OFFICER

Deputy Division Director's Review of NDA 21-770

Original New Drug Application

Submission Date:	May 27, 2004
Review Completed:	March 31, 2005
Deputy Division Director:	Wiley A. Chambers, MD
Trademark:	Alphagan [redacted]
Established Name:	brimonidine tartrate ophthalmic solution
Applicant:	Allergan, Inc. 2525 Dupont Drive P.O. Box 19534
Pharmacologic Category:	Alpha-2 agonist
Proposed Indication:	Reduction of intraocular pressure
Dosage Form:	Ophthalmic solution
Route of Administration:	Topical ocular
NDA Drug Classification:	3S

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I. Recommendations

A. Recommendation on Approvability

NDA 21-770 is approvable for lowering intraocular pressure in patients with open-angle glaucoma or ocular hypertension following the resolution of the manufacturing deficiencies, manufacturing compliance with current Good Manufacturing Practices (cGMPs) and submission of revised labeling.

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 reformulation of brimonidine tartrate ophthalmic solution, lowering the concentration to 0.1%. The application included the results of a clinical bioequivalence study (190342-021) in which the proposed new drug product demonstrated bioequivalence with Alphagan (brimonidine tartrate ophthalmic solution) 0.2%.

B. Efficacy

Efficacy is based on the applicant's studies supporting NDA 20-613, Alphagan (brimonidine tartrate ophthalmic solution), 0.2% and NDA 21-262, Alphagan P (brimonidine tartrate ophthalmic solution), 0.15%. Study 190342-021 provides a link to Alphagan through clinical bioequivalence. The Division's definition of clinical bioequivalence with respect to efficacy (95% confidence interval within 1mmHg at the majority of time points and within 1.5mmHg at all times points in a 3 month study evaluating peak and trough time points) has been met.

C. Safety

Safety is based on the applicant's studies in NDA 20-613, Alphagan (brimonidine tartrate ophthalmic solution), 0.2% and NDA 21-262, Alphagan P (brimonidine tartrate ophthalmic solution), 0.15%. Study 190342-021 provides a link to Alphagan through clinical bioequivalence and no new issues of safety have been identified in the clinical bioequivalence study.

D. Dosing, Regimen, and Administration

In the clinical studies evaluating safety, efficacy and bioequivalence, one drop of brimonidine tartrate ophthalmic solution was administered three times daily to the affected eye.

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

Reviews have been completed from Chemistry/Manufacturing, Non-clinical Pharmacology/Toxicology, Microbiology (sterility assurance), Clinical Pharmacology, and the Division of Drug Marketing, Advertising and Communications (DDMAC). There are several unresolved issues with respect to sterility assurance and compliance with current good manufacturing practices at the manufacturing facility in Waco, TX. This facility was not found to be in compliance with cGMPs and was issued a 483 in January 2005. These issues involved in the inspection will need to be satisfactorily resolved prior to approval of the application.

IV. Labeling

Labeling is based on the labeling of Alphagan (brimonidine tartrate ophthalmic solution) 0.2% and Alphagan P (brimonidine tartrate ophthalmic solution) 0.15% and includes formulation specific changes. Additional proposed claims with respect to the contribution of the drug product's increased pH to the bioavailability of the drug substance have not been supported in the application and have not been included in the proposed labeling.

Review by the Division of Medication Errors and Technical Support in the Office of Drug Safety, does not recommend the use of the name Alphagan [redacted] The recommendation is based on belief that the [redacted]' is "not a necessary modification of the proprietary name, Alphagan and may be misinterpreted to mean purite free since it does not use the modifier 'P' ." The review suggests that the products may be sufficiently differentiated with the prominent labeling of their respective strengths. The Division disagrees with this assessment. The products Alphagan, Alphagan P and Alphagan [redacted] have been found to be equivalent to each other with respect to safety and efficacy in spite of their different concentrations of brimonidine. Efforts to differentiate them with prominent labeling of their respective strengths would be potentially misleading. Confusion between the products, even if it is to occur, is not likely to be clinically meaningful because of the clinical equivalence. It is not clear that failing to include the letter P in the trademark will necessarily be interpreted to mean purite free and the inclusion or exclusion of purite has never been shown to have a more clinically meaningful effect on the drug product compared to any other preservative. To the extent that the letter P has differentiated the products in the past, the letters [redacted] should do the same in the future and the Division believes that it is an appropriate level of distinction. Additionally, there is no evidence that the modifier [redacted] has resulted in any clinical harm as it has been applied to another of Allergan's products. [redacted]

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/s/

Wiley Chambers
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MEDICAL OFFICER

Wiley Chambers
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MEDICAL OFFICER

CLINICAL REVIEW

Application Type	NDA 21-770
Submission Number	000
Submission Code	Original
Letter Date	5/27/04
Stamp Date	6/1/04
PDUFA Goal Date	4/1/05
Reviewer Name	Martin P. Nevitt, M.D., M.P.H.
Review Completion Date	3/18/05
Established Name	Brimonidine Tartrate Ophthalmic Solution, 0.1%
(Proposed) Trade Name	Alphagan [redacted]
Therapeutic Class	Alpha 2 -agonist
Applicant	Allergan, Inc. 2525 Dupont Drive P.O. Box 19534 Irvine, CA 92623-9534 714-246-4500 FAX: 714-246-4272 Lewis Gryziewicz 714-246-6088
Priority Designation	S

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

From a clinical perspective, NDA 21–770 is recommended for approval for the treatment of elevated intraocular pressure (IOP) in patients with open angle glaucoma or ocular hypertension after resolution of the manufacturing issues.

The Applicant has failed to provide adequate information regarding equipment and [redacted] validation and the procedure for conducting media fills. Failure to address the microbiology deficiencies could result in an increased risk of product contamination during aseptic processing.

The bioequivalence trial (study 190342-021) supports approval of this drug product. The primary efficacy endpoint, mean intraocular pressure, is demonstrated to be equivalent when comparing brimonidine tartrate ophthalmic solution 0.1% (referred to as Brimonidine Purite) to a previously approved drug, brimonidine tartrate ophthalmic solution 0.2% (referred to as Alphagan). Equivalence is defined as the two sided 95% confidence interval being less than 1.5 mmHg at each direct group comparison over multiple times over a three month period and being less than 1.0 mmHg for the majority of direct group comparisons. Alphagan (NDA 20-613) was first approved in 1996 for the reduction of elevated IOP in patients with open-angle glaucoma and/or ocular hypertension.

The recommended dosing regiment is one drop in the affected eye(s) 3 times a day.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

No additional clinical trials or postmarketing surveillance studies are required.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Established Name	brimonidine tartrate ophthalmic solution, 0.1% (referred to as Brimonidine Purite)
(Proposed) Trade Name	Alphagan [redacted]
Therapeutic Class	alpha 2 –agonist

Glaucoma is a disease characterized by optic nerve damage and visual field loss often associated with increased intraocular pressure (IOP). IOP is an important risk factor for developing open angle glaucoma. Ocular hypertension is a condition characterized by increased IOP in the absence of identifiable optic nerve damage and visual field loss.

In this clinical trial, reduction in IOP was the proposed primary efficacy endpoint studied in patients with open angle glaucoma or ocular hypertension. The proposed indication for this drug product was for the reduction of intraocular pressure in male or female patients, 2 years or older, with open angle glaucoma or ocular hypertension.

With prior FDA agreement, a single clinical trial comparing brimonidine tartrate ophthalmic solution, 0.1% (Brimonidine Purite) with brimonidine tartrate ophthalmic solution, 0.2% (Alphagan) would be acceptable as clinical support if Brimonidine Purite demonstrated equivalence to Alphagan. Alphagan was previously approved September 6, 1996 in NDA 20-613).

Study 190342-021 was a multicenter, double masked, randomized, parallel-group design with 8 scheduled visits: prestudy, baseline, week 2, week 6, and months 3, 6, 9 and 12. The study objectives were to evaluate the safety and efficacy of Brimonidine Purite 3 times daily compared with Alphagan 3 times daily for 3 months (plus 9-month, masked extension) in patients with glaucoma or ocular hypertension. Additional safety and secondary parameters examined were visual acuity, visual fields, cup/disc ratio, pregnancy, biomicroscopy/ophthalmoscopy and adverse events.

1.3.2 Efficacy

The primary measure of efficacy was mean IOP at exam visits, hours 0, 2 and 8 on day 0, weeks 2 and 6, and month 3. IOP was unadjusted for central corneal thickness and the average IOP from both eyes was used (in this study all patients were treated bilaterally).

The demographic characteristics between the two ITT treatment groups (Brimonidine Purite and Alphagan groups) had no significant differences. The efficacy results of the trial demonstrated there were no statistically significant differences between the 2 treatment groups at any follow-up timepoint for mean IOP at each visit and at each time interval. This new formulation, Brimonidine Purite, demonstrated equivalence to Alphagan in IOP lowering ability.

1.3.3 Safety

The most frequently reported adverse events ($\geq$ 5% in either treatment group) were allergic conjunctivitis, conjunctival hyperemia, eye pruritis and oral dryness. Differences between the 2 treatment groups were noted for 3 individual adverse events: the incidence of oral dryness and asthenia were lower with Brimonidine Purite than with Alphagan [(3/215 vs. 13/218) and (2/215 vs. 10/218), respectively] while the incidence of eye pain was significantly higher with Brimonidine Purite than with Alphagan (6/215 vs. 0/218). The incidence of eye pain, 2.8% (6/215), was higher for the Brimonidine Purite group but the number of affected patients was

small. The differences are not statistically significant after correction for the multiple comparisons.

Few serious adverse events were reported in the clinical trial. None of the events were ocular, and none were considered to be related to the study medications; there were no deaths. The incidence of serious adverse events were similar in each treatment group. No serious adverse events were reported for more than 1% in any treatment group.

Additional safety parameters examined were visual acuity, visual fields, cup/disc ratio and biomicroscopy/ophthalmoscopy. For visual acuity and visual fields there were no statistically significant difference between the 2 treatment groups and no clinically relevant patterns or trends were noted. For the cup/disc ratio, no patients in either treatment group showed improvement or worsening from baseline.

1.3.4 Dosing Regimen and Administration

Dose-response efficacy has been studied previously with brimonidine in concentrations ranging from 0.08% to 0.5% (NDAs 20-613 and 21-262). In addition, clinical pharmacokinetic studies have evaluated systemic exposure to brimonidine and have shown it to be safe when administered at concentrations higher than 0.1%.

The recommended dosing schedule is one drop, applied topically to the affected eye(s), three times a day in patients diagnosed with glaucoma or ocular hypertension.

1.3.5 Drug-Drug Interactions

There were no important drug-drug interactions noted that would affect the product's clinical use.

1.3.6 Special Populations

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

No patients with hepatic or renal impairment were studied.

There are no adequate and well-controlled studies in pregnant woman. It is not known whether this drug is excreted in human milk; although in animal studies brimonidine tartrate was excreted in breast milk.

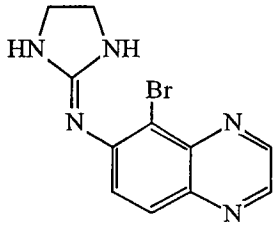
Previously, in a well-controlled clinical study conducted in pediatric glaucoma patients (ages 2 to 7 years) the most commonly observed adverse events with brimonidine tartrate 2% (Alphagan) dosed three times daily were somnolence (50% - 83%) in patients ages 2 to 6 and decreased alertness. In patients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

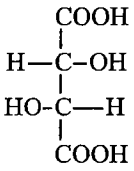
discontinued from the study due to somnolence. The safety and effectiveness of Brimonidine tartrate ophthalmic solution have not been studied in pediatric patients below the age of 2 years. Brimonidine tartrate ophthalmic solution is not recommended for use in patients under the age of 2 years. No additional pediatric studies are planned.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Established Name	brimonidine tartrate ophthalmic solution, 0.1%
(Proposed) Trade Name	Alphagan [redacted]
Therapeutic Class	Alpha 2 -agonist
Formulation	$C_{11}H_{10}BrN_5 \cdot C_4H_6O_6$





Proposed Indication	Reduction of intraocular pressure in patients 2 years or older with open angle glaucoma or ocular hypertension

Composition of Brimonidine Purite Ophthalmic Solution 0.1%

Ingredient	Function	Grade	Concentration (% w/v)	Concentration (mg/ml)
Brimonidine Tartrate	Drug Substance	N/A	0.1	1.0
Carboxymethylcellulose sodium (CMC)	[redacted]	USP	[redacted]	[redacted]
Stabilized Oxychloro Complex (Purite®)		N/A		
Boric Acid		NF		
Sodium Borate [redacted]		NF		
Sodium Chloride		USP		
Potassium Chloride		USP		
Calcium Chloride [redacted]		USP		
Magnesium Chloride [redacted]		USP		
Sodium Hydroxide 1N		NF		
Hydrochloric Acid 1N		NF		
Purified Water		USP		

Reviewer's Comments:

Brimonidine is currently approved as Alphagan (brimonidine tartrate ophthalmic solution) 0.2% under NDA 20-613, and Alphagan P (brimonidine tartrate ophthalmic solution) 0.15% under NDA 21-262, for lowering intraocular pressure in patients with open angle glaucoma or ocular hypertension. Brimonidine tartrate ophthalmic solution, 0.1% (Brimonidine Purite) has a pH of 7.7. This new formulation with a higher pH results in an increased percentage of non-ionized brimonidine which is asserted by the applicant to be more membrane permeable. As a result, a reduced concentration may maintain therapeutic effects while decreasing ocular and systemic exposure.

2.2 Currently Available Treatment for Indications

There are currently available numerous topical treatments for open angle glaucoma and ocular hypertension either as first or second line therapy. These treatments include Beta-adrenergic antagonists (beta-blockers), Adrenergic agonists, Parasympathomimetic (miotic) agents, Carbonic anhydrase inhibitors and Prostaglandin analogues.

This NDA application is for Brimonidine tartrate ophthalmic solution, 0.1%, an Alpha 2-adrenergic agonist.

2.3 Availability of Proposed Active Ingredient in the United States

Brimonidine is currently approved as ALPHAGAN (brimonidine tartrate ophthalmic solution 0.2%), NDA 20-613, and ALPHAGAN P (brimonidine tartrate ophthalmic solution 0.15%), NDA 21-262, for lowering intraocular pressure in patients with open angle glaucoma or ocular hypertension.

The following table provides a comparison of the previously approved formulations of brimonidine with Brimonidine Purite the formulation proposed in this NDA:

Brimonidine Concentration, pH, and Preservatives in Brimonidine Purite 0.1%, Ophthalmic Solution, Alphagan P, and Alphagan

Product Name	Brimonidine (% w/v)	Purite (ppm)	BAK (ppm)	Target pH
Brimonidine Purite (Brimonidine tartrate **0.1%**); (Proposed Tradename: Alphagan	0.1			7.7
Alphagan P (Brimonidine tartrate **0.15%**)	0.15			7.2
Alphagan (Brimonidine tartrate **0.2%**)	0.2			6.5

The clinical study forming the basis of this NDA, is an equivalence trial, that compared Brimonidine Purite 0.1% with Alphagan (brimonidine tartrate ophthalmic solution 0.2%).

2.4 Important Issues With Pharmacologically Related Products

There have been no additional safety issues raised with this class of agents outside of those identified in this review.

In an effort to maintain effective IOP reduction while enhancing safety and tolerability, Brimonidine tartrate ophthalmic solution 0.1% at a pH of 7.7 has been developed. This new formulation with a higher pH results in an increased percentage of non-ionized brimonidine which is asserted by the applicant to be more membrane permeable. The increased ocular absorption allows for a lower concentration of 0.1% while maintaining the aqueous humor drug levels. As a result, this reduced concentration has the potential to maintain therapeutic effects while decreasing ocular and systemic exposure.

2.5 Presubmission Regulatory Activity

A Pre-NDA meeting was held October 20, 2003, the sponsor requested clarification from the FDA if an NDA can be based on a single clinical study. The FDA responded a single phase 3 study comparing brimonidine tartrate 0.1% (Brimonidine Purite) with brimonidine tartrate 0.2% (Alphagan) is acceptable if it demonstrates equivalence to Alphagan. Based on this same meeting the following changes were made to the analyses listed in the study protocol:

- The primary efficacy variable was changed from IOP adjusted for central corneal thickness to unadjusted IOP; adjusted IOP was changed to a secondary efficacy variable.

- For the FDA, equivalence rather than the combined strategy of non-inferiority and superiority tests were used to analyze the primary efficacy variable.

2.6 Other Relevant Background Information

The sponsor has not submitted any international labeling regarding approval or pending approval for Brimonidine.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

NDA 21-770 is approvable pending the resolution of microbiology deficiencies listed below:

The Applicant has failed to provide adequate information regarding equipment and [redacted] validation and the procedure for conducting media fills. Failure to address the microbiology deficiencies could result in an increased risk of product contamination during [redacted] processing.

3.2 Animal Pharmacology/Toxicology

There were no significant findings from pre-clinical pharmacology or toxicology reviews that would affect the clinical outcome.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The submitted clinical study report and protocol for study 190342-021 and relevant literature reports were reviewed. The submitted study report forms the basis for the majority of this application.

The entire application was submitted in electronic format.

A PubMed electronic literature search was performed to supplement the review, and no new information was found.

4.2 Tables of Clinical Studies

Phase 3 Glaucoma/Ocular Hypertension Study Utilized in M.O. Safety and Efficacy Review

Study ID	# Study Center Location	Study Start Status (Date) Enrollment Total/Goal	Design Control Type	Study & Control Drugs Dose, Route, and Regimen	Study Objective	# Entered/ Completed 3 month	Duration	M/F mean age (range) Race	Diagnosis Inclusion Criteria	Primary Efficacy Endpoint
190342-021	27 centers USA	16 May 2003 3-month completion: 11 Dec. 2003 433 enrolled 384 planned	Multi-center, double-masked, parallel group, stratified random-ization Active control	Brimon-idine Purite 0.1% (pH 7.7) Alphagan (Brimon-idine tartrate) 0.2%	Evaluate safety/ efficacy of Brimon-idine Purite 0.1% compared with Alphagan	Brimon-idine Purite 0.1% 215/183 Alphagan 218/168	3 month plus 9 month. masked ex-tension	M 187 43.2% F 246 56.8% 62.4 yrs. (19-93) C 341 78.8% B 49 11.3% A 2 0.5% H 35 8.1% O 6 1.4%	Glaucoma or ocular hyper-tension ≥ 18 yrs. Day 0/ IOP ≥ 22 and ≤ 34 mm Hg in each eye Asym-metry between eyes ≤ 5 mm Hg Visual acuity ≥ 20/80 in each eye	IOP at hours 0, 2 and 8 of weeks 2, 6 and month 3

M = Male, F = Female; C = Caucasian, B = Black, A = Asian, H = Hispanic, O = Other; yrs = years, hr = hours, IOP = intraocular pressure

Reviewer's Comments:

The design of the clinical trial and the number of centers is acceptable.

4.3 Review Strategy

The submitted clinical study report and protocol for study 190342-021 and relevant literature reports were reviewed. The submitted study report forms the basis of this application.

The entire application was submitted in electronic format except for Module 1 Volume 1 which was submitted electronically and as a paper Desk Copy.

4.4 Data Quality and Integrity

The medical officer has reviewed all Case Report Forms for discontinued subjects in study 190342-021. There were no problems noted with data quality and integrity.

4.5 Compliance with Good Clinical Practices

The data was reviewed for consistency with other applications in this class. No special methods were used.

All trials were conducted under the review of approved Institutional Review Board committees. Investigators used an informed consent form that was appropriate for the trial.

4.6 Financial Disclosures

The applicant has adequately disclosed financial arrangements with clinical investigators as recommended in the FDA guidance for industry on *Financial Disclosure by Clinical Investigators.*

There is no evidence to suggest that the results of the studies were impacted by any financial payments.

5 CLINICAL PHARMACOLOGY (FROM THE CLINICAL PHARMACOLOGY REVIEW)

5.1 Pharmacokinetics

Pharmacokinetic parameters of brimonidine in human plasma after 1 dose (day 1) or 19 doses (day 7) of Brimonidine-Purite 0.1% or 0.2% TID to each eye of healthy subjects. Parameters are expressed as mean ± SD (N).

Formulation	Day	C_{max} (pg/mL)	t_{max} (hr)	$AUC_{0-t\ last}$ (pg·hr/mL)	$AUC_{0-\infty}$ (pg·hr/mL)	$t_{1/2}$ (hr)
0.1%	1	23.3 ± 14.1 (13)	1.54 ± 0.66 (13)	79.3 ±47.8(12)	NC[1]	NC[1]
	7	30.0 ± 17.8 (13)	1.50 ± 0.68 (13)	127 ± 87 (13)	136 ± 85 (12)	188 ± 0.81 (12)
0.2%	1	48.4±35.1 (13)	1.77± 0.60 (13)	211± 147 (13)	NC[1]	NC[1]
	7	64.7 ± 37.8 (13)	1.35± 0.94 (13)	245 ± 124 (13)	245 ± 124 (13)	1.95 ± 0.63 (13)

Since the pharmacokinetic parameters are dose proportional, the sponsor extrapolated the pharmacokinetic parameters for 0.15% Brimonidine-Purite™ from the data for 0.1% and 0.2% Brimonidine-Purite™ solutions, as shown in the following table.

Formulation	Day[1]	N	C_{max} (pg/mL)	$AUC_{interval}$[2] (pg·hr/mL)	AUC_{0-24}[3] (pg·hr/mL)
Brimonidine-Purite 0.2% TID	7	13 (7M + 6F)	64.7 ± 37.8	245 ± 124	735
Alphagan 0.2% BID	10	7 (3M + 4F)	58.5 ± 29.9	309 ± 142	618
Brimonidine-Purite 0.15% TID[4]	7	13 (7M + 6F)	47.4	191	572
Alphagan 0.2% TID[5]	10	7 (3M + 4F)	NE[6]	NE[6]	927

Overall, the systemic exposure of brimonidine from the Brimonidine-Purite™ formulation appears to be lower than the marketed formulation ALPHAGAN® formulation. For this lower strength (0.1%) formulation of Brimonidine-Purite,™ the levels would be expected to be proportionally lower.

5.2 Pharmacodynamics

Not applicable to this application.

5.3 Exposure-Response Relationships

Not applicable to this application.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

The proposed indication is for the reduction of intraocular pressure in male or female patients, 2 years old or more, with open angle glaucoma or ocular hypertension.

6.1.1 Methods

The submitted clinical study report and protocol for study 190342-021 and literature reports were reviewed.

The entire application was submitted in electronic format.

A PubMed electronic literature search was performed to supplement the review, and no new information was found.

6.1.2 General Discussion of Endpoints

Reduction in IOP was the efficacy parameter studied in patients with open angle glaucoma or ocular hypertension.

The primary efficacy endpoint for study 190342-021 was the mean IOP (unadjusted for central corneal thickness and the average IOP from both eyes was used in the analyses) measured using Goldmann applanation tonometry. Results for the Intent-To-Treat group, which included all randomized patients, and the per protocol populations were provided in the current NDA.

IOP measurements were taken at the prestudy visit, at hours 0, 2 and 8 on day 0, weeks 2 and 6, and months 3, 6, and 12 visits, and at hours 0 and 2 at the month 9 visit. IOP was measured at least twice in each eye. If the difference of the first 2 measurements was $\leq$ 2 mm Hg, the average of these 2 measurements was used as the IOP data for this eye. If the difference was > 2 mm Hg, a third measurement was to be taken, and the median of these 3 measurements was used as the IOP data for this eye. In this study all patients were treated bilaterally. For the analysis, the average IOP from both eyes was used.

6.1.3 Study Design

One clinical trial, study 190342-021, is provided in this Medical Officer's review. The information from this clinical study follows:

Principle Investigators and Patients Enrolled
Study 190342-021

Principal Investigator	Center Number	City and State	Number Randomized & Enrolled
Richard Bennison, M.D.	2973	Wenatchee, WA	16
David Brodstein, M.D.	3283	Ogden, UT	7
David Cooke, M.D.	2232	St. Joseph, MI	32
Joel M. Corwin, M.D.	4082	Ventura, CA	26
E. Randy Craven, M.D.	2027	Littleton, C.O.	18
Douglas Day, M.D.	2851	Atlanta, GA	14
Monte Dirks, M.D.	2078	Rapid City, SD	32
Harvey DuBiner, M.D.	2450	Morrow, CA	19
Richard Evans, M.D.	2975	San Antonio, TX	11
Jon Robert Fishburn, M.D.	4090	Boise, ID	5
Walter Fried, M.D.	2860	Gurnee, IL	8
David Gendelman, M.D.	3293	Burlington, MA	15
Christopher Lin, M.D.	3636	Redding, CA	16
Jeffrey Lozier, M.D.	2981	San Diego, CA	14
Michael Rotberg, M.D.	2037	Charlotte, NC	12
Kenneth Sall, M.D.	2707	Bellflower, CA	30
Howard Schenker, M.D.	2429	Rochester, N.Y.	22
Elizabeth Sharpe, M.D.	1995	Charleston, SC	17
Mark Sherwood, M.D.	2118	Gainesville, FL	5
Robert Shields, M.D.	1724	Denver, CO	6
Steve Simmons, M.D.	1655	Singerlands, NY	7
Joseph Sokol, M.D.	2952	Waterbury, CT	7
Alfred Solish, M.D.	0202	Pasadena, CA	14
Richard T. Sturm, M.D.	1587	Lynbrook, NY	16
Jeffrey Whitsett, M.D.	3185	Houston, TX	12
Robert Williams, M.D.	2710	Louisville, KY	27
David Wirta, M.D.	3276	Newport Beach, CA	25

Reviewer's comments:

It is preferred to have at least 10 subjects per center to allow for an interaction analysis.

Inclusion Criteria:

The following were requirements for entry into the study:

1. male or female, at least 18 years of age
2. patient had ocular hypertension, chronic open angle glaucoma, chronic angle closure glaucoma with patent iridotomy/iridectomy, pseudoexfoliative glaucoma or pigmentary glaucoma in both eyes
3. patient was likely to be controlled on monotherapy
4. patient required bilateral treatment
5. best-corrected Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity score equivalent to a Snellen score of 20/80 or better in each eye at the baseline visit
6. written informed consent and written authorization for use or release of health and research study information were obtained prior to any study procedures
7. patient was able and willing to follow study instructions and likely to complete all required visits
8. baseline (day 0/hour 0) IOP greater than or equal to 22 mm Hg and less than or equal to 34 mm Hg in each eye, and asymmetry of IOP between the eyes was not greater than 5 mm Hg
9. at baseline (day 0), negative urine pregnancy test for females of childbearing potential prior to randomization
10. at baseline (day 0), 2 reliable visual fields on file before dosing: the first visual field could have been performed at the prestudy visit or within 6 months of the prestudy visit; the second visual field should have been performed at the baseline visit or within 1 week prior to the baseline visit
11. at baseline (day 0), patient had been appropriately washed-out of all IOP-lowering medication(s)

Reviewer's comments:

*Patient enrollment was based on IOP **unadjusted** for corneal thickness (unadjusted IOP).*

*Efficacy outcome analysis utilized **adjusted** and **unadjusted** IOP measurements. (The difference in **unadjusted** IOP = Pre-op **unadjusted** IOP – Post-op **unadjusted** IOP. The difference in **adjusted** IOP = Pre-op **adjusted** IOP – Post-op **adjusted** IOP.)*

Exclusion Criteria:

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

1. uncontrolled systemic disease (eg, diabetes)
2. patient with severe cardiovascular disease should not have been enrolled unless his/her disease was controlled and clearance had been obtained from the treating primary care physician or cardiologist
3. females who were pregnant, nursing, or planning a pregnancy or who were of childbearing potential who were not using a reliable means of contraception
4. clinically relevant, abnormally low or high blood pressure or pulse rate for age

5. known allergy or sensitivity to the study medications or their components
6. intermittent use of oral, injectable, or topical ophthalmic steroids within 21 days prior to the prestudy visit, or anticipated use during the study
7. contraindications to brimonidine therapy, concurrent use of monoamine oxidase (MAO) inhibitor therapy
8. recent (within previous 2 months) or anticipated alteration of existing chronic treatment or introduction of treatment with agents which could have a substantial effect on IOP (including, but not necessarily limited to, systemic adrenergic agents including beta-adrenergic blocking agents [eg, propranolol, metoprolol, nadolol, timolol, and atenolol])
9. concurrent use or anticipated treatment with antidepressants which affect noradrenergic transmissions (eg, tricyclic antidepressants, mianserin) or adrenergic-augmenting psychotropic drugs (eg, desipramine, amitriptyline)
10. any active ocular disease other than glaucoma (eg, uveitis, ocular infections, or severe dry eye); however, patients with cataracts, age-related macular degeneration, or background diabetic retinopathy may have been enrolled at the discretion of the investigator
11. corneal abnormalities that would have precluded accurate readings with an applanation tonometer
12. anticipated wearing of contact lenses during the study; use of soft lenses should have been discontinued at least 2 days prior to day 0, and use of rigid gas permeable (RGP) or hard contact lenses should have been discontinued at least 1 week prior to day 0
13. required use of ocular medications during the study other than the study medications; occasional use of artificial tears or topical antihistamines was allowed
14. refractive surgery, laser trabeculoplasty, or other laser surgery within the past 3 months, or other intraocular surgery (eg, uncomplicated cataract surgery) within the past 6 months, or filtering surgery within the past 12 months
15. visual field loss which, in the opinion of the investigator, was functionally significant or evidence of progressive visual field loss within the last year
16. contraindication to pupil dilation
17. current enrollment in an investigational drug or device study or participation in such a study within 30 days prior to day 0
18. patient had a condition or was in a situation which, in the investigator's opinion, may have put the patient at a significant risk, may have confounded study results, or may have interfered significantly with patient's participation in the study

Reviewer's Comments:

Acceptable.

Study Plan

The study objectives were to evaluate the safety and efficacy of brimonidine tartrate ophthalmic solution 0.1% 3 times daily compared with an active control, brimonidine tartrate ophthalmic

solution 0.2% (Alphagan) 3 times daily for 3 months (plus 9-month, masked extension) in patients with glaucoma or ocular hypertension.

The study was a multicenter, double-masked, randomized, parallel-group design with 8 scheduled visits: prestudy, baseline (day 0), week 2, week 6, and months 3, 6, 9, and 12. Intraocular pressure was the primary efficacy endpoint. At the prestudy visit, IOP was measured once. At other visits, with the exemption of the month 9 visit, diurnal IOP was measured at approximately 08:00 (hour 0), 10:00 (hour 2), and 16:00 (hour 8). At the month 9 visit, IOP was measured at hour 0 and hour 2 only. Patients who were chronically treated with ocular hypotensive medications were required to undergo appropriate washout periods prior to study entry to minimize any residual effects of other active ocular hypotensive medications.

Qualified patients with chronic glaucoma or ocular hypertension were then stratified into 2 groups based on the day 0/hour 0 IOP averaged between two eyes: IOP $\leq$ 25 mm Hg or IOP > 25 mm Hg. With each stratum, patients were randomly assigned Brimonidine 0.1% or 0.2% in an even allocation (1:1). Study medications were dosed 3 times daily at approximately 08:00, 14:00, and 20:00. Patients were instructed not to use the study medication on the morning of a study visit; the morning dose was to be taken after all hour 0 examinations were completed.

The data was analyzed after all patients completed the month 3 visit or exited the study prior to month 3. The 3-month analyses are considered primary. An analysis on all 12-month data will be performed as a safety and efficacy update.

Reviewer's Comments:

Acceptable. Refer to section 7.2.9 for information regarding the 120-day safety update.

Efficacy Endpoint

The primary measure of efficacy was mean IOP at exam visits hours 0, 2 and 8 on day 0, weeks 2 and 6, and month 3. IOP was unadjusted for central corneal thickness and the average IOP from both eyes was used (in this study all patients were treated bilaterally).

Secondary efficacy analyses included IOP adjusted for prestudy central corneal thickness, IOP change from baseline, adjusted IOP change from baseline.

Safety measures analyzed included adverse events, heart rate, blood pressure, visual acuity, biomicroscopy of anterior segment, visual field examination, ophthalmoscopy, including reporting of cup/disc ratio, and urine pregnancy test. Safety data were analyzed for the safety population.

The ITT population included all randomized patients; the PPP included all patient data with no major protocol violations; and the safety population included all randomized patients who received at least one dose of study medication.

The data were analyzed after all patients completed the month 3 visit or exited the study prior to month 3. The 3-month analyses are considered primary. An analysis on all 12-month data were performed as a safety and efficacy update.

Reviewer's Comments:

Acceptable. Refer to section 6.1.4 for a review of the primary efficacy endpoint.

Schedule of Visits and Measurements

Day	Time[a]	AE	HR, BP[b]	VA[b]	Biomicroscopy[b]	IOP	Visual Fields	Pregnancy[c]	Corneal Thick[b]	Ophthalmoscopy[d]
Prestudy[e]				X	X	X	X[f]		X	X
WASHOUT PERIOD (2 days TO 8 weeks)										
Day 0 (baseline)	T_0		X	X	X	X	X[g]	X		
	T_0 + 2h					X				
	T_0 + 8h					X				
DOSING BEGAN IN THE EVENING OF THE BASELINE VISIT BETWEEN 19:00 and 21:00										
Week 2	T_0	X	X	X	X	X				
	T_0 + 2h					X				
	T_0 + 8h					X				
Week 6	T_0	X	X	X	X	X				
	T_0 + 2h					X				
	T_0 + 8h					X				
Month 3	T_0	X	X	X	X	X	X	X		
	T_0 + 2h					X				
	T_0 + 8h					X				X
Month 6	T_0	X	X	X	X	X				
	T_0 + 2h					X				
	T_0 + 8h					X				
Month 9	T_0	X	X	X	X	X				
	T_0 + 2h					X				
Month 12	T_0	X	X	X	X	X	X	X		
	T_0 + 2h					X				
	T_0 + 8h					X				X

AE = adverse event, BP = blood pressure, IOP = intraocular pressure, HR = heart rate, VA = visual acuity

a T_0 = time of hour 0 measurements between 07:00 and 09:00 at all visits. On day 0, T_0 + 2h and T_0 + 8h were 2 hours and 8 hours after T_0 IOP measurement, respectively. At all other visits, T_0 + 2h and T_0 + 8h were 2 hours and 8 hours after morning dose (considered as T_0), respectively.

b performed before IOP measurements at T_0

c pregnancy test performed on female study patients of child-bearing potential

d performed after the IOP measurement and visual field examination (if performed)

e includes written informed consent, authorization, and complete medical and ophthalmic histories (to be updated at the day 0 visit)

f prestudy visual field performed at the prestudy visit or within 6 months prior; examinations must have been reliable, performed with Humphrey full-threshold 24-2 or [redacted] standard automated perimetry testing, preferably a [redacted] was not accepted)
g day 0 (baseline) visual field performed up to 1 week prior to the baseline visit or at the baseline visit
h central corneal thickness measurements of each eye were measured at the prestudy visit only using an ultrasonic pachymeter.

Reviewer's Comments:

Acceptable.

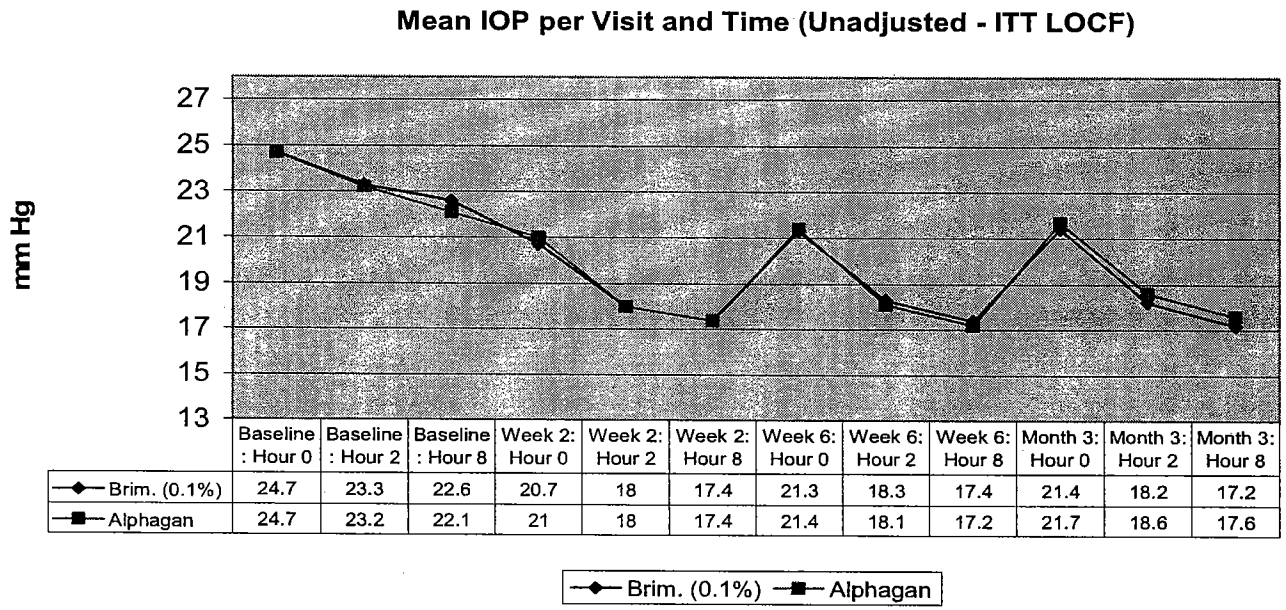
Patient Population

Patient Group	Enrolled		Month 3 Exit Status	
	Brimonidine 0.1% Number of Patients	Alphagan Number of Patients	Brimonidine 0.1% Number of Patients	Alphagan Number of Patients
ITT:	215	218	183	168
Discontinued	0	0	32	50
Safety:	215	218	183	168
Discontinued	0	0	32	50
PPP:	205	208	173	160
Discontinued	10	10	32	48

Reviewer's Comments:

The ITT population provides the basis of the primary efficacy data set. All case report forms for discontinued patients were reviewed by the medical officer. There are nearly equal numbers of patients discontinued for each group (ITT, Safety and PPP) and for each drug product.

6.1.4 Efficacy Findings



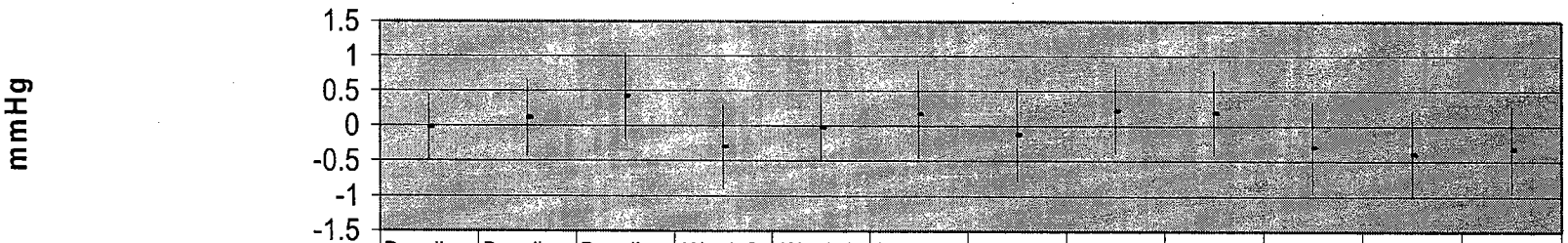
	Baseline : Hour 0	Baseline : Hour 2	Baseline : Hour 8	Week 2: Hour 0	Week 2: Hour 2	Week 2: Hour 8	Week 6: Hour 0	Week 6: Hour 2	Week 6: Hour 8	Month 3: Hour 0	Month 3: Hour 2	Month 3: Hour 8
Brim. (0.1%)	24.7	23.3	22.6	20.7	18	17.4	21.3	18.3	17.4	21.4	18.2	17.2
Alphagan	24.7	23.2	22.1	21	18	17.4	21.4	18.1	17.2	21.7	18.6	17.6

Reviewer's Comments:

IOP, the primary efficacy endpoint, is based on the mean IOP (average IOP between both eyes and unadjusted for corneal thickness).

There were no statistically significant differences between the 2 treatment groups at any follow-up timepoint. This new formulation, Brimonidine 0.1%, demonstrated equivalence to Alphagan for the primary endpoint. Equivalence is defined as the two sided 95% confidence interval being less than 1.5 mmHg at each direct group comparison over multiple times over a three month period and being less than 1.0 mmHg for the majority of direct group comparisons.

Mean Difference (Unadjusted Brim. - Alph.) with 95% CI [ITT LOCF]



	Baseline: Hour 0	Baseline: Hour 2	Baseline: Hour 8	Week 2: Hour 0	Week 2: Hour 2	Week 2: Hour 8	Week 6: Hour 0	Week 6: Hour 2	Week 6 : Hour 8	Month 3: Hour 0	Month 3: Hour 2	Month 3: Hour 8
Lower CI	-0.47	-0.44	-0.2	-0.9	-0.5	-0.46	-0.78	-0.4	-0.42	-0.96	-1	-0.95
Upper CI	0.44	0.66	1.04	0.3	0.54	0.8	0.54	0.84	0.8	0.35	0.21	0.29
• Mean Difference (Brim. - Alph.)	-0.02	0.11	0.42	-0.3	-0.02	0.17	-0.12	0.22	0.19	-0.3	-0.4	-0.33

Reviewer's Comments:

Within each treatment group, the mean decreases from baseline IOP were statistically significant at each follow-up timepoint ($p<0.001$).

During follow-up, the mean change from baseline IOP of the Brimonidine 0.1% group was found to be equivalent to the Alphagan group. (i.e., the 95% confidence interval crosses zero at all timepoints measured).

6.1.5 Clinical Microbiology

This drug is not an antimicrobial. Not applicable.

6.1.6 Efficacy Conclusions

The primary efficacy endpoint (unadjusted) demonstrates Brimonidine 0.1% to be equivalent to Alphagan. Equivalence is defined as the two sided 95% confidence interval being less than 1.5 mmHg at each direct group comparison over multiple times over a three month period and being less than 1.0 mmHg for the majority of direct group comparisons.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

The submitted clinical study report and protocol for study 190342-021 and literature reports were reviewed. The submitted study report was reviewed and forms the basis of this application.

The entire application was submitted in electronic format.

A PubMed electronic literature search was performed to supplement the review and no new information was found.

The medical officer has reviewed all Case Report Forms for discontinued subjects in the study (190342-021).

The data was reviewed for consistency with other applications in this class. No special methods were used.

All trials were conducted under the review of approved Institutional Review Board committees. Investigators used an informed consent form that was appropriate for the respective trials

7.1.1 Deaths

No deaths occurred during the study.

7.1.2 Other Serious Adverse Events

Serious Adverse Events
Number (%) of Patients by Descending Order per Percentage
Either Treatment Group

Adverse Event	Brim. 0.1% N=215 N (%)	Alphagan N = 218 N (%)
Overall	5 (2.3%)	4 (1.8%)
Cholecystitis	1 (0.5%)	0 (0.0%)
Chest pain	1 (0.5%)	0 (0.0%)
Bone fracture	1 (0.5%)	0 (0.0%)
Angina pectoris	1 (0.5%)	0 (0.0%)
Coronary artery disorder	1 (0.5%)	0 (0.0%)
Transient ischemic attack	0 (0.0%)	1 (0.5%)
Atrial fibrillation	0 (0.0%)	1 (0.5%)
Cerebrovascular accident	0 (0.0%)	1 (0.5%)
Intestinal perforation	0 (0.0%)	1 (0.5%)

Few serious adverse events were reported in the clinical trial. None of the events were ocular, and none were considered by the investigators to be related to the study medications; there were no deaths.

Reviewer's Comments:

The rate of serious adverse events were similar in each treatment group. No serious adverse events were reported for more than 1% in any treatment group.

7.1.3 Dropouts and Other Significant Adverse Events

Discontinued Patients

Brim. = Brimonidine 0.1%; Alph. = Alphagan

Patient	TX Exposure (days)	TX Group	Reason
1655-5081	90	Brim	Adverse event allergic conjunctivitis
2078-1003	92	Brim	Adverse event allergic conjunctivitis
2078-1009	70	Brim	Adverse event allergic conjunctivitis
2078-1014	87	Brim	Adverse event allergic conjunctivitis
2078-5006	85	Brim	Lack of efficacy
2078-5197	33	Brim	Adverse event allergic conjunctivitis
2707-1081	108	Brim	Personal reasons due to school schedule/withdrew consent
2710-1101	15	Brim	Lack of efficacy
2710-1271	50	Brim	Lack of efficacy
2710-1279	7	Brim	Protocol violation medication stopped to reassess baseline IOP
2710-5055	26	Brim	Adverse event follicular conjunctivitis
2851-1055	22	Brim	Adverse event eye irritation
2851-1059	84	Brim	Adverse event allergic conjunctivitis
2851-5033	29	Brim	Lack of efficacy
2851-5189	92	Brim	Lack of efficacy
2232-1027	42	Brim	Adverse event conjunctival hyperemia foreign body sensation
2450-1174	106	Brim	Adverse event allergic conjunctivitis
2450-1178	84	Brim	Adverse event allergic conjunctivitis
2860-5229	92	Brim	Adverse event follicular conjunctivitis
2952-1223	91	Brim	Lack of efficacy
2952-1226	20	Brim	Lack of efficacy

Discontinued Patients (continued)

Patient	TX Exposure (days)	TX Group	Reason
2952-5109	43	Brim	Lack of efficacy
2973-1210	9	Brim	Adverse event allergic conjunctivitis
2973-5103	92	Brim	Lack of efficacy
2981-1154	20	Brim	Adverse event allergic conjunctivitis
2981-1157	45	Brim	Personal reasons
2981-1160	78	Brim	Adverse event allergic conjunctivitis
3276-1298	44	Brim	Adverse event allergic conjunctivitis
3636-1148	11	Brim	Adverse event allergic conjunctivitis
3636-1152	73	Brim	Adverse event allergic conjunctivitis
3636-5073	95	Brim	Lack of efficacy
4090-1198	26	Brim	Adverse event allergic conjunctivitis
0202-1230	48	Alph	Adverse event conjunctival hyperemia
0202-1236	2	Alph	Adverse event allergic conjunctivitis
1587-1100	11	Alph	Adverse event somnolence/lethargy
1995-1190	132	Alph	Personal Reasons
1995-5201	15	Alph	Other patient decision
2027-1360	52	Alph	Adverse event allergic conjunctivitis
2027-1382	84	Alph	Adverse event allergic conjunctivitis
2037-1244	15	Alph	Adverse event eye pruritis lid edema
2078-1007	11	Alph	Adverse event allergic conjunctivitis
2078-5003	42	Alph	Adverse event allergic conjunctivitis
2078-5008	99	Alph	Lack of efficacy
2078-5199	43	Alph	Lack of efficacy
2078-5200	44	Alph	Lack of efficacy

Discontinued Patients (continued)

Patient	Tx Exposure (days)	Tx Group	Reason
2232-1028	94	Alph	Personal reasons patient stopped medication at primary care doctor's request, as unsure of its role in patient's sinus problem
2232-5022	55	Alph	Adverse event; asthenia
232-5023	71	Alph	Adverse event allergic conjunctivitis
2450-1169	37	Alph	Adverse event allergic conjunctivitis
2450-5218	91	Alph	Lack of efficacy
2450-5219	92	Alph	Lack of efficacy
2707-1088	3	Alph	Adverse event eye pruritis
2707-1089	34	Alph	Adverse event cerebrovascular accident
2710-1104	93	Alph	Adverse event oral dryness
2710-1108	61	Alph	Adverse event allergic rash (legs/body)
2710-1278	74	Alph	Adverse event allergic conjunctivitis
2710-5056	50	Alph	Lack of efficacy
2710-5133	8	Alph	Personal Reasons withdrew consent
2851-1056	43	Alph	Lack of efficacy
2851-1058	43	Alph	Lack of efficacy
2851-5034	14	Alph	Adverse event asthenia
2860-5039	32	Alph	Lack of efficacy
2952-1224	55	Alph	Adverse event allergic conjunctivitis
2981-1158	89	Alph	Adverse event somnolence
2981-1159	69	Alph	Adverse event allergic conjunctivitis
2981-1333	92	Alph	Adverse event allergic conjunctivitis
3185-1183	90	Alph	Adverse event allergic conjunctivitis

Discontinued Patients (continued)

Patient	Tx Exposure (days)	Tx Group	Reason
3185-5090	90	Alph	Adverse event erythema eyelid
3185-5210	69	Alph	Adverse event conjunctival hyperemia conjunctival edema
3276-1305	42	Alph	Adverse event allergic conjunctivitis
3276-1307	46	Alph	Adverse event allergic conjunctivitis
3283-1339	22	Alph	Adverse event depression
3293-1129	50	Alph	Adverse event allergic conjunctivitis
3636-1146	92	Alph	Lack of efficacy
3636-1150	92	Alph	Adverse event allergic conjunctivitis
3636-1356	48	Alph	Adverse event increased intraocular pressure
3636-5075	92	Alph	Lack of efficacy
3636-5076	99	Alph	Lack of efficacy
4082-1117	4	Alph	Adverse event allergic conjunctivitis
4082-1121	1	Alph	Adverse event allergic keratoconjunctivitis
4082-5059	47	Alph	Lack of efficacy

Reviewer's Comments:

Discontinued patients comprised 14.9% (32/215) of the Brimonidine 0.1% group and 22.9% (50/218) of the Alphagan group by the month 3 visit. Compared with the Brimonidine 0.1% group, a greater percentage of patients in the Alphagan group discontinued for lack of efficacy and from adverse events. Refer also to section 7.1.3.1 for discontinued subjects and reason for discontinuing.

7.1.3.1 Overall profile of dropouts

Patients	Brim 0.1% N (%)	Alphagan N (%)
Total Randomized	215 (100%)	218 (100%)
Completed Month 3	183 (85.1%)	168 (77.1%)
Discontinued:	32 (14.9%)	50 (22.9%)
Lack of Efficacy	10 (4.7%)	13 (6.0%)
Adverse Event	19 (8.8%)	33 (15.1%)
Personal Reasons	2 (0.9%)	3 (1.4%)
Protocol Violation	1 (0.5%)	0 (0.0%)
Other (unspecified)	0 (0.0%)	1 (0.5%)

7.1.3.2 Adverse events associated with dropouts

Compared with the Brimonidine 0.1% group, a greater percentage of patients in the Alphagan group discontinued for lack of efficacy and due to adverse events.

7.1.3.3 Other significant adverse events

Refer to section 7.1.2.

7.1.4 Other Search Strategies

Case Report Forms for all discontinued subjects were reviewed by the medical officer.

7.1.5 Common Adverse Events

Number (%) of Patients with Adverse Events Reported by ≥ 2% of Patients Either Treatment Group

BODY SYSTEM Preferred Term	Brim 0.1% N = 215 N (%)	Alphagan N = 218 N (%)
Overall	108 (50.2%)	125 (57.3%)
BODY AS A WHOLE		
Infection (unspecified)	6 (2.8%)	1 (0.5%)
Asthenia	2 (0.9%)	10 (4.6%)
Headache	2 (0.9%)	5 (2.3%)
CARDIOVASCULAR		
Hypertension	3 (1.4%)	8 (3.7%)
DIGESTIVE		
Oral dryness	3 (1.4%)	13 (6.0%)
Periodontal abscess	0 (0.0%)	5 (2.3%)
NERVOUS		
Somnolence	2 (0.9%)	5 (2.3%)
SPECIAL SENSES		
Allergic conjunctivitis	22 (10.2%)	23 (10.6%)
Conjunctival hyperemia	16 (7.4%)	21 (9.6%)
Eye pain	6 (2.8%)	0 (0.0%)
Eye pruritis	4 (1.9%)	11 (5.0%)
Conjunctival folliculosis	4 (1.9%)	6 (2.8%)
Burning sensation in eye	2 (0.9%)	5 (2.3%)

Reviewer's Comments:

The most frequently reported events (≥ 5% in either treatment group) were allergic conjunctivitis, conjunctival hyperemia, eye pruritis and oral dryness. Differences between the 2 treatment groups were noted for 3 individual adverse events: the incidence of oral dryness and asthenia were lower with Brimonidine 0.1% than with Alphagan while the incidence of eye pain was significantly higher with Brimonidine 0.1% than with Alphagan. After correction for multiplicity, none of the differences were statistically significant.

7.1.5.1 Eliciting adverse events data in the development program

Adverse events were assessed at each scheduled visit (Day 0 through Month 3) and at any unscheduled visits. Duration, investigator's perceived relationship between event and study drug, action(s) taken and outcome were recorded on the Adverse Event form.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

The applicant's categorization of events is comparable to the investigators' categorization of events when case report forms are reviewed. Investigator recorded verbatim terms were coded to preferred terms and grouped by body system using the Allergan modified COSTART (Coding Symbols for Thesaurus of Adverse Reaction Terms; US FDA, 1985) dictionary.

7.1.5.3 Incidence of common adverse events

Refer to section 7.1.5. There is only one clinical trial, therefore there is no pooled data.

7.1.5.4 Common adverse event tables

Refer to section 7.1.5. There is only one clinical trial; therefore there is no pooled data.

7.1.5.5 Identifying common and drug-related adverse events

See Table 7.1.5.

7.1.5.6 Additional analyses and explorations

Not applicable. There were no additional analyses and explorations performed regarding adverse events.

7.1.6 Less Common Adverse Events

Refer to section 7.1.5.

7.1.7 Laboratory Findings

Not applicable. Clinical laboratory data (hematology, chemistry, urinalysis) were not collected in this study.

7.1.7.1 Overview of laboratory testing in the development program

Not applicable. Clinical laboratory data (hematology, chemistry, urinalysis) were not collected in this study.

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

Not applicable. Clinical laboratory data (hematology, chemistry, urinalysis) were not collected in this study.

7.1.7.3 Additional analyses and explorations

Not applicable. Clinical laboratory data (hematology, chemistry, urinalysis) were not collected in this study.

7.1.7.4 Special assessments

Not applicable. Clinical laboratory data (hematology, chemistry, urinalysis) were not collected in this study.

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

Vital signs (heart rate and blood pressure) were assessed at baseline and at any follow up visit. There was no statistically significant within or between-group differences in the change from baseline for these vital signs at any follow-up visit.

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

Refer to section 7.1.8.1.

7.1.8.3 Standard analyses and explorations of vital signs data

Refer to section 7.1.8.1.

7.1.9 Electrocardiograms (ECGs)

7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

Not applicable. Based on the fund of knowledge regarding this group of therapeutics, no ECGs were performed.

7.1.10 Immunogenicity

Not applicable. Drug product is not expected to induce immunogenicity.

7.1.11 Human Carcinogenicity

Not applicable. Brimonidine tartrate did not have positive animal carcinogenicity, mutagenic or cytogenic findings to warrant a systemic assessment of all human tumors reported during drug development.

7.1.12 Special Safety Studies

Additional safety parameters examined were visual acuity, visual fields, cup/disc ratio and biomicroscopy/ophthalmoscopy. For visual acuity and visual fields there were no statistically significant difference between the 2 treatment groups and no clinically relevant patterns or trends were noted. For the cup/disc ratio no patients in either treatment group showed improvement or worsening from baseline. The only statistically between-group difference was a lower incidence of lid edema in the Brimonidine 0.1% group (1.4%) versus the Alphagan group (5.0%).

7.1.13 Withdrawal Phenomena and/or Abuse Potential

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

7.1.14 Human Reproduction and Pregnancy Data

The drug was not studied in pregnancy. No pregnancies were reported during the clinical trial. It is not known whether this drug is excreted in human milk; although in animal studies brimonidine tartrate was excreted in breast milk.

7.1.15 Assessment of Effect on Growth

Brimonidine tartrate ophthalmic solution 0.1% has not been studied in the pediatric population.

Alphagan (brimonidine tartrate ophthalmic solution 0.2%) has been studied in a well-controlled clinical study conducted in pediatric glaucoma patients (ages 2 to 7 years) the most commonly observed adverse effects were somnolence and decreased alertness. The safety and effectiveness of brimonidine tartrate ophthalmic solution have not been studied in pediatric patients below the age of two years. Brimonidine tartrate ophthalmic solution is not recommended for use in pediatric patients under the age of 2 years.

7.1.16 Overdose Experience

No information is available on overdosage of Brimonidine Purite during clinical trials in adults.

In postmarketing surveillance through 31 December 2003, there have been 7 cases involving Alphagan (brimonidine tartrate ophthalmic solution 0.2%) and Alphagan P (brimonidine tartrate ophthalmic solution 0.15%) in which events were coded as "accidental overdosage" (MedDRA – Version 6.1). Four reports were of events that occurred when the medication was administered topically to the eyes; none of the events were serious and each patient recovered without sequelae. Three reports involved accidental oral ingestion; each patient recovered without sequelae. Note that symptoms of brimonidine overdose such as hypotension, bradycardia,

hypothermia, and apnea have been reported in a few neonates receiving Alphagan as part of medical treatment of congenital glaucoma.

7.1.17 Postmarketing Experience

Refer to section 7.1.16.

7.2 Adequacy of Patient Exposure and Safety Assessments

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

The clinical study report, clinical protocol and literature reports were reviewed. The entire application was submitted in electronic format.

Modules 1, 2 and 5 were reviewed in depth. Proposed draft labeling and Case Report Forms for discontinued subjects were provided electronically.

Refer to Section 4.2 for a table of the clinical study.

7.2.1.1 Study type and design/patient enumeration

Data from one phase 3 clinical study has been submitted in support of this NDA. Refer to Section 4.2 for a table of the clinical study.

7.2.1.2 Demographics

Demographics for All Randomized Patients in Study 190342-021

Brim Purite N= 215; Alphagan N= 218

Category	Treatment Group			
	Brim Purite		Alphagan	
	N	%	N	%
Sex				
Male	91	42.3	96	44.0
Female	124	57.7	122	56.0
Age Class				
< 45 yrs	15	7.0	16	7.3
45 – 65 yrs	117	54.4	106	48.6
> 65 yrs	83	38.6	96	44.0
Race				
Black	25	11.6	24	11.0
Non-Black	190	88.4	194	89.0
Caucasian	173	80.5	168	77.1
Asian	1	0.5	1	0.5
Hispanic	13	6.0	22	10.1
Other	3	1.4	3	1.4
Iris Color				
Dark	84	39.1	99	45.4
Light	131	60.9	119	54.6
Diagnosis (Study Eye)				
Glaucoma	135	62.8	144	66.1
Ocular Hyp.	75	34.9	70	32.1
Mixed	5	2.3	4	1.8
Corneal Pachymetry (microns)				
Mean	568.7		562.5	
SD	35.25		39.27	
Min	448		466	
Max	656		661	

Reviewer's Comments:

There were no significant differences between treatment groups in baseline demographic characteristics.

7.2.1.3 Extent of exposure (dose/duration)

Cumulative Patient Distribution by Scheduled Visit
Intent–to-Treat Population (ITT)

Exam Visit	Brim Purite	Alphagan	Total
Day 0	215	218	433
Week 2	209	207	416
Week 6	202	195	397
Month 3	183	168	351

Reviewer's Comments:

The mean duration of treatment exposure was similar in both groups. For the Brimonidine Purite group mean treatment exposure was 87.8 days; mean exposure was 84.1 days for the Alphagan group.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

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

7.2.2.1 Other studies

One phase 3 clinical trial (study 190342-021) was submitted in this NDA. Brimonidine tartrate has been previously approved as brimonidine tartrate 0.2% (Alphagan), NDA 20-613, and brimonidine tartrate 0.15% (Alphagan P), NDA 21-262, both were referenced in the submission.

7.2.2.2 Postmarketing experience

Alphagan had been marketed for approximately 8.5 years and Alphagan P for 3 years with a low overall rate of reported spontaneous events (0.003%). Alphagan is no longer marketed although generic versions of Alphagan are marketed. The postmarketing data is consistent with the safety profile from the clinical studies, and provides reassurance that no new safety issues have emerged with prolonged use.

7.2.2.3 Literature

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

7.2.3 Adequacy of Overall Clinical Experience

An adequate number of subjects, including adequate demographic subsets, were exposed to the drug product in a well-controlled, randomized, clinical trial. The doses and durations of exposure were adequate to assess safety for the intended use.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

Not applicable. Refer to Pharmacology/Toxicology review.

7.2.5 Adequacy of Routine Clinical Testing

Not applicable. Clinical laboratory data (hematology, chemistry, urinalysis) were not collected in this study.

The methods and ophthalmologic tests used and their frequency were adequate to effectively monitor the subject population.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

Renal excretion was the primary route of elimination for brimonidine and its metabolites. After an oral radiolabeled dose administration to human volunteers, approximately 74% of the dose was excreted in the urine and approximately 13% of the dose in the feces (a total of 87% excreted within 120 hours). Refer to the Clinical Pharmacologist review for more detail.

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

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

7.2.8 Assessment of Quality and Completeness of Data

The submitted safety database appeared adequate and complete for the class of pharmacologic class of agents.

7.2.9 Additional Submissions, Including Safety Update

The 120-day safety update was submitted to FDA on September 30, 2004. The study objectives were to evaluate the safety and efficacy of Brimonidine 0.1%, 3 times daily compared with Alphagan (brimonidine tartrate ophthalmic solution 0.2%) 3 times daily for 3 months (plus 9-month, masked extension) in patients with glaucoma or ocular hypertension.

With the longer duration of treatment exposure during this follow-up period, the incidence of adverse events increased over what was previously reported for the 3-month data submitted with the NDA. The update overall incidence of adverse events regardless of causality was 66.0% (142/215) for the Brimonidine 0.1% group and 72.5% (158/218) for the Alphagan group. The most frequently reported adverse events (≥ 5% in either treatment group) were allergic conjunctivitis, conjunctival hyperemia, infection (Body as a Whole), hypertension, eye pruritus, and oral dryness. Adverse events reported by ≥ 2% in either treatment group are summarized below:

Number (%) of Patients with Adverse Events Reported by ≥ 2% of Patients Either Treatment Group for 120 Day Safety Update

BODY SYSTEM Preferred Term	Brim Purite N = 215 N (%)	Alphagan N = 218 N (%)
BODY AS A WHOLE		
Infection	11(5.1%)	2 (0.9%)
Accidental injury	6 (2.8%)	2 (0.9%)
Asthenia	3 (1.4%)	10 (4.6%)
Headache	4 (1.9%)	6 (2.8%)
CARDIOVASCULAR		
Hypertension	4 (1.9%)	15 (6.9%)
DIGESTIVE		
Nausea	5 (2.3%)	1 (0.5%)
Oral dryness	3 (1.4%)	13 (6.0%)
Periodontal abscess	0 (0.0%)	6 (2.8%)
METABOLIC/NUTRITIONAL		
Hypercholesterolemia	4 (1.9%)	5 (2.3%)
NERVOUS		
Somnolence	2 (0.9%)	5 (2.3%)
RESPIRATORY		
Bronchitis	3 (1.4%)	6 (2.8%)
SPECIAL SENSES		
Allergic conjunctivitis	39 (18.1%)	43 (19.7%)
Conjunctival hyperemia	20 (9.3%)	25 (11.6%)
Conjunctival folliculosis	7 (3.3)	8 (3.7%)
Eye pain	6 (2.8%)	0 (0.0%)
Eye dryness	5 (2.3%)	6 (2.8%)
Follicular conjunctivitis	5 (2.3%)	1 (0.5%)
Eye pruritis	4 (1.9%)	13 (6.0%)
Burning sensation in eye	2 (0.9%)	6 (2.8%)

Statistically significant differences between the 2 treatment groups were noted for 6 individual adverse events: the incidence of hypertension, oral dryness, eye pruritus, and periodontal abscess were lower with Brimonidine 0.1% than with Alphagan.

The observed incidence rate of infection (Body as a Whole) was higher for the Brimonidine 0.1% group (5.1% (11/215)) compared with the Alphagan group (0.9% (2/218)). The vast majority of these occurrences were mild in severity. The incidence of eye pain at 2.8% was for the Brimonidine 0.1% group. The number of patients affected was small (6 of 215) and was not believed to be clinically relevant.

Reviewer's Comments:

The overall incidence of discontinuation due to adverse events resulted in a statistically significant difference (p = 0.004) between groups, with a lower proportion of patients discontinuing in the Brimonidine 0.1% group (19.5%) as compared with the Alphagan group (31.7%).

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

Statistically significant differences between 2 treatment groups were noted for 3 individual adverse events: the incidences of oral dryness and asthenia were significantly lower with Brimonidine 0.1% than with Alphagan ($p \leq 0.020$) while the incidence of eye pain was significantly higher with Brimonidine 0.1% than with Alphagan.

Reviewer's Comments:

Refer to comments to section 7.1.5.5.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

7.4.1.1 Pooled data vs. individual study data

Not applicable. This NDA is a single study phase 3 clinical trial.

7.4.1.2 Combining data

Not applicable. This NDA is a single study phase 3 clinical trial.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

Dose-response efficacy has been studied previously with brimonidine in concentrations ranging from 0.08% to 0.5% (NDAs 20-613 and 21-262). In addition, clinical pharmacokinetic studies have evaluated systemic exposure to brimonidine, and have shown it to be safe when administered at concentrations higher than 0.1%.

The recommended dosing schedule is one drop, applied topically to the affected eye(s), three times a day in patients diagnosed with glaucoma or ocular hypertension.

8.2 Drug-Drug Interactions

There were no important drug-drug interactions noted that would affect the product's clinical use.

Although specific drug interactions have not been studied, 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 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 in humans can lead to resulting interference with the IOP lowering effect. Caution is advised in patients taking tricyclic antidepressants which can affect the metabolism and uptake of circulating amines.

8.3 Special Populations

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

No patients with hepatic or renal impairment were studied; caution should be used in treating these patients.

There are no adequate and well-controlled studies in pregnant woman. It is not known whether this drug is excreted in human milk; although in animal studies brimonidine tartrate was excreted in breast milk.

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 2% (Alphagan) dosed three times daily were somnolence (50% - 83%) in patients ages 2 to 6 and decreased alertness. In patients 7 years of age or older (> 20 Kg), somnolence appears to occur less frequently (25%). Brimonidine tartrate is not recommended for use in patients under the age of 2 years.

8.4 Pediatrics

No additional pediatric studies are planned. Refer to section 8.3.

8.5 Advisory Committee Meeting

Not applicable.

8.6 Literature Review

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

8.7 Postmarketing Risk Management Plan

Not applicable. The applicant did not submit a postmarketing risk management plan, nor is one needed.

8.8 Other Relevant Materials

A consultation is currently pending with the Division of Medication Errors and Technical Support (DDMAC) regarding the tradename provided by the sponsor, Alphagan [redacted]

9 OVERALL ASSESSMENT

9.1 Conclusions

The results for brimonidine tartrate 0.1% in clinical study 190342-021 show equivalence in its IOP lowering effect (the primary efficacy endpoint) with respect to brimonidine tartrate 0.2% (Alphagan, previously approved in NDA 20-613).

9.2 Recommendation on Regulatory Action

From a clinical perspective, NDA 21-770 is recommended for approval for the treatment of elevated intraocular pressure (IOP) in patients 2 years or older with glaucoma or ocular hypertension after resolution of the manufacturing issues.

The Applicant has failed to provide adequate information regarding equipment and [redacted] validation and the procedure for conducting media fills. Failure to address the microbiology deficiencies could result in an increased risk of product contamination during [redacted] processing.

9.3 Recommendation on Postmarketing Actions

Not applicable. Further postmarketing actions are not required.

9.4 Labeling Review

9.5 Comments to Applicant

None. No postmarketing actions are recommended.

7 Page(s) Withheld

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