# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**21-262**

# MEDICAL REVIEW

# Medical Officer's Review of NDA 21-262

| | | | |
|---|---|---|---|
| NDA 21-262 | | Submission: | 12/22/00 |
| Medical Officer's Review #6 | | Review Completed: | 12/22/00 |

| | |
|---|---|
| **Proposed Tradename:** | ALPHAGAN® P |
| **Generic Name:** | Brimonidine-Purite Ophthalmic Solution 0.15% |
| **Chemical Name:** | 5-bromo-6-(2-imidazolidinylideneamino) quinoxaline L-tartrate |
| **Sponsor:** | Allergan<br>2525 Dupont Drive<br>P.O. Box 19534<br>Irvine, California 92623<br><br>Attn: Lewis Gryziewicz |
| **Pharmacologic Category:** | Alpha 2-agonist |
| **Proposed Indication:** | Reduction of intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension |
| **Submitted:** | Proposed labeling |

Allergan, Inc.

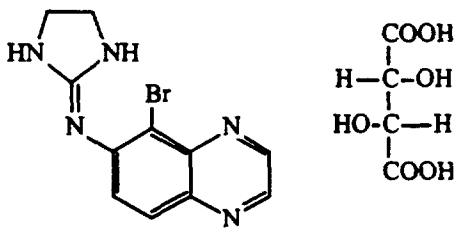
**ALPHAGAN® P**

(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:** sodium carboxymethylcellulose; sodium borate; boric acid; sodium chloride; potassium chloride; calcium chloride; magnesium chloride; purified water; 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 2-5mmHg.

## 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 thromboangiitis 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 **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.

**Pregnancy:** Teratogenic effects: Pregnancy Category B.

Reproductive studies performed in rats with oral doses of 0.66 mg base/kg revealed no evidence of impaired fertility or 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; 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:**

Safety and effectiveness in pediatric patients have not been established. Agitation, apnea, bradycardia, convulsions, cyanosis, depression, dyspnea, emotional instability, hypotension, hypothermia, hypotonia, hypoventilation, irritability, lethargy, somnolence, and stupor have been reported in pediatric patients receiving brimonidine tartrate 0.2%.

**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 pruritus.

Adverse events occurring in approximately 5-9% of the subjects included: burning sensation, conjunctival folliculosis, 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.

## 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.

## HOW SUPPLIED:

**ALPHAGAN® P** is supplied sterile in opaque teal LDPE plastic bottles with droppers with purple high impact polystyrene (HIPS) caps as follows:

| | |
|---|---|
| 5 mL in 10mL 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**



Irvine, CA 92612, U.S.A.

**Conclusions/Recommendations**

The enclosed labeling is acceptable. Following resolution of any chemistry/manufacturing issues, NDA 21-262 is recommended for approval for lowering intraocular pressure in patients with ocular hypertension or open-angle glaucoma.

Jennifer D. Harris, MD
Medical Officer, Ophthalmology

Orig. NDA 21-262
HFD-550/Div Files
HFD-550/MO/Harris
HFD-550/SMO/Chambers
HFD-550/Acting Div Dir/Bull
HFD-550/Biopharm/Tandon
HFD-550/Chem/Rodreguez
HFD-550/PharmTox/Mukherjee
HFD-550/PM/Gorski

# Medical Officer's Review of NDA 21-262

| | | |
|---|---|---|
| NDA 21-262 | Submission: | 12/13/00 |
| Medical Officer's Review #4 | Review Completed: | 12/18/00 |

| | |
|---|---|
| **Proposed Tradename:** | ALPHAGAN® P |
| **Generic Name:** | Brimonidine-Purite Ophthalmic Solution 0.15% |
| **Chemical Name:** | 5-bromo-6-(2-imidazolidinylideneamino) quinoxaline L-tartrate |
| **Sponsor:** | Allergan<br>2525 Dupont Drive<br>P.O. Box 19534<br>Irvine, California 92623<br>Attn: Lewis Gryziewicz |
| **Pharmacologic Category:** | Alpha 2-agonist |
| **Proposed Indication:** | Reduction of intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension |
| **Submitted:** | Revised labeling |

Allergan, Inc.

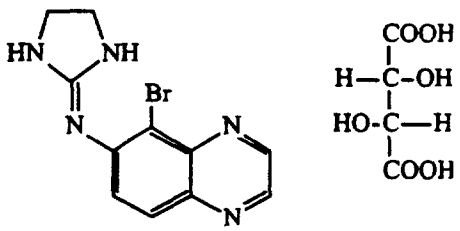
**ALPHAGAN® P**

(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:** sodium carboxymethylcellulose; sodium borate; boric acid; sodium chloride; potassium chloride; calcium chloride; magnesium chloride; purified water; 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% effectively lowers IOP in patients with open-angle glaucoma or ocular hypertension by approximately 2-5mmHg.

## 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 thromboangiitis 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 **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.

**Pregnancy:** Teratogenic effects: Pregnancy Category B.

Reproductive studies performed in rats with oral doses of 0.66 mg base/kg revealed no evidence of impaired fertility or 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; 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:**

Safety and effectiveness in pediatric patients have not been established. Agitation, apnea, bradycardia, convulsions, cyanosis, depression, dyspnea, emotional instability, hypotension, hypothermia, hypotonia, hypoventilation, irritability, lethargy, somnolence, and stupor have been reported in pediatric patients receiving brimonidine tartrate 0.2%.

**Geriatric Use:**

No overall difference has 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: [redacted] burning sensation, conjunctival folliculosis, [redacted] hypertension, oral dryness, and visual disturbance.

Events occurring in approximately 1-4% of subjects included: allergic reaction, asthenia, asthma, 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.

## 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.

## HOW SUPPLIED:

**ALPHAGAN® P** is supplied sterile in opaque teal LDPE plastic bottles with droppers with purple high impact polystyrene (HIPS) caps as follows:

| | |
|---|---|
| 5 mL in 10mL 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**



Irvine, CA 92612, U.S.A.

Jennifer D. Harris, MD
Medical Officer, Ophthalmology

Orig. NDA 21-262
HFD-550/Div Files
HFD-550/MO/Harris
HFD-550/SMO/Chambers
HFD-550/Acting Div Dir/Bull
HFD-550/Biopharm/Tandon
HFD-550/Chem/Rodreguez
HFD-550/PharmTox/Mukherjee
HFD-550/PM/Gorski

**APPEARS THIS WAY ON ORIGINAL**

Medical Officer's Review of NDA 21-262

| | |
|---|---|
| **NDA 21-262**<br>**Medical Officer's Review # 5** | **Submission Date:** June 29, 2000<br>**Received Date:** June 30, 2000<br>**Review Date:** December 19, 2000 |
| **Sponsor:** | Allergan<br>2525 Dupont Drive<br>P.O. Box 19534 |
| **Generic Name:** | brimonidine tartrate ophthalmic solution 0.15% |
| **Drug:** | Alphagan® P |
| **Pharmacologic Category:** | Alpha 2-agonist |
| **Proposed Indication:** | Lowering of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension |
| **Investigator's Financial Disclosure Information:** | Submitted in Volume 1.1 |

**Reviewer's Comments:**

*The original NDA submission identified two investigators with financial interests who participated in one of the clinical studies (190342-007) included in this NDA submission. If these investigators were excluded, there would be no significant impact on the result of the study in which the Investigators participated.*

**Recommendation:**

*Following resolution of any chemistry/manufacturing issues and labeling issues, NDA 21-262 is recommended for approval for lowering intraocular pressure in patients with ocular hypertension or open-angle glaucoma.*

Jennifer D. Harris, M.D.
Medical Officer

cc: NDA 21-262
HFD-550/Div Files
HFD-550/CSO/Gorski
HFD-550/MO/Harris
HFD-550/SMO/Chambers
HFD-550/acting Div Dir/Bull
HFD-550/Pharm/Mukherjee
HFD-550/Chem/Rodriquez
HFD-550/Biopharm/Tandon

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

**Medical Officer's Review of NDA 21-262**

| | |
|---|---|
| NDA 21-262 | Submission: 11/2/00 |
| Medical Officer's Review # 3 | Review Completed: 11/27/00 |

| | |
|---|---|
| **Proposed Tradename:** | Alphagan-P |
| **Generic Name:** | Brimonidine-Purite Ophthalmic Solution 0.15% |
| **Chemical Name:** | 5-bromo-6-(2-imidazolidinylideneamino) quinoxaline L-tartrate |
| **Sponsor:** | Allergan<br>2525 Dupont Drive<br>P.O. Box 19534<br>Irvine, California 92623<br>Attn: Lewis Gryziewicz |
| **Pharmacologic Category:** | Alpha 2-agonist |
| **Proposed Indication:** | Reduction of intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension |
| **Submitted:** | Revised labeling |

**Reviewer's Comments:**
*Recommended additions are shown by underlining and recommended deletions are shown by strikethrough lines.*

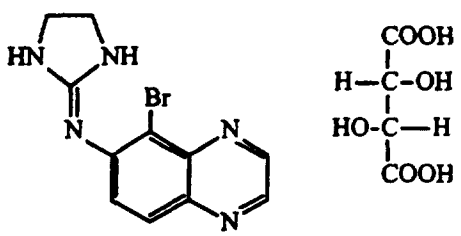
[redacted] Allergan, Inc.

[redacted]ALPHAGAN-P™
(brimonidine tartrate ophthalmic solution) 0.15%

Sterile

**DESCRIPTION**

~~TRADENAME~~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-~~imidazolidinylideneamine~~[redacted] quinoxaline L-tartrate. It is an off-white to pale yellow[redacted]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, [redacted] 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 [redacted] ALPHAGAN-P™ contains:
**Active ingredient:** brimonidine tartrate 0.15% (1.5 mg/mL).
**Preservative:** Purite® 0.005% (0.05 mg/mL)
**Inactives:** sodium carboxymethylcellulose; sodium borate; boric acid; sodium chloride; potassium chloride; calcium chloride; magnesium chloride; purified water; with hydrochloric acid and/or sodium hydroxide to adjust pH.

## CLINICAL PHARMACOLOGY

Mechanism of action:

[redacted] ALPHAGAN-P™ is an alpha adrenergic receptor agonist. It has a peak ocular hypotensive effect occurring at two hours post-dosing. [redacted] 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. [redacted]

Pharmacokinetics:

[redacted] 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. [redacted]

In humans, systemic metabolism of brimonidine is extensive. [redacted] It is metabolized primarily by the liver. [redacted] 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. [redacted]

[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.

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% effectively lowers IOP in patients with open-angle glaucoma or ocular hypertension 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 thromboangiitis 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 and times, respectively, the plasma drug concentration estimated in humans treated with one drop 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.

Pregnancy: Teratogenic effects: Pregnancy Category B.

Reproductive studies performed in rats with oral doses of 0.66 mg base/kg revealed no evidence of impaired fertility or harm to the fetus due to ALPHAGAN-P. Dosing at this level produced an exposure that is [redacted] times higher than the exposure seen in humans following multiple ophthalmic doses.

There are no adequate and well-controlled studies in pregnant women, [redacted] in animal studies, brimonidine crossed the placenta and entered into the fetal circulation to a limited extent. [redacted] ALPHAGAN-P™ should be used during pregnancy only if [redacted] 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; although in animal studies brimonidine tartrate was excreted in breast milk. [redacted] 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:
Safety and effectiveness in pediatric patients have not been established. Agitation, apnea, bradycardia, convulsions, cyanosis, depression, dyspnea, emotional instability, hypotension, hypothermia, hypotonia, hypoventilation, irritability, lethargy, somnolence, and stupor have been reported in pediatric patients receiving brimonidine tartrate 0.2%.

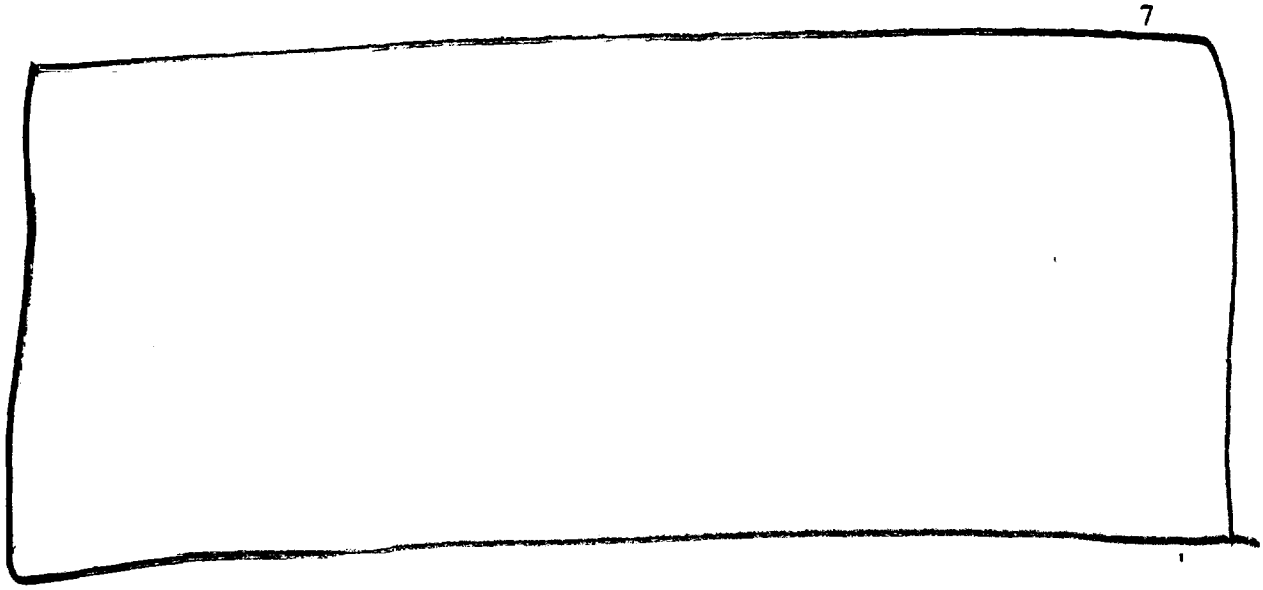
[redacted]

Geriatric Use:
No overall difference has been observed between elderly and other adult patients.

[redacted]

**ADVERSE REACTIONS**

[redacted]



Adverse events occuring in approximately 10 – 20 % of the subjects included allergic conjuctivitis , conjuctival hyperemia and eye prutitus.

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

Events occuring in approximately 1 – 4% of subjects included allergic reaction, asthenia, blepharitis, bronchitis, conjunctival edema, conjunctival hemorrhage, conjunctivitis, cough, dizziness, dyspepsia, dypsnea, 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, worsened visual acuity.

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

**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.

**HOW SUPPLIED:**

ALPHAGAN-P™ is supplied sterile in opaque teal LDPE plastic bottles with droppers with purple high impact polystyrene (HIPS) caps as follows:

5 mL in 10mL 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 [redacted] between 15-25°C (59-77°F)

**Rx Only**
**ALLERGAN**

Irvine, CA 92612, U.S.A.

Jennifer D. Harris, MD
Medical Officer, Ophthalmology

Orig. NDA 21-262
HFD-550/Div Files
HFD-550/MO/Harris
HFD-550/SMO/Chambers
HFD-550/Acting Div Dir/Bull
HFD-550/Biopharm/Tandon
HFD-550/Chem/Rodreguez
HFD-550/PharmTox/Mukherjee
HFD-550/PM/Gorski

**Medical Officer's Review of NDA 21-262**
120-Day Safety Update

| | |
|---|---|
| NDA 21-262 | Submission: 11/2/00 |
| Medical Officer's Review #2 | Review Completed: 11/13/00 |

| | |
|---|---|
| **Proposed Tradename:** | Alphagan-P |
| **Generic Name:** | Brimonidine-Purite Ophthalmic Solution 0.15% |
| **Sponsor:** | Allergan<br>2525 Dupont Drive<br>P.O. Box 19534<br>Irvine, California 92623-9534 |
| **Pharmacologic Category:** | Alpha 2-agonist |
| **Proposed Indication:** | Lowering of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension |
| **Dosage Form and Route of Administration:** | Ophthalmic suspension for topical ocular administration |
| **Submitted:** | Pooled 120-Day Safety Information for Protocols 190342-007 and 190342-008 |

**Table 1** – Incidence of Adverse Events Reported by ≥ 1% of Patients in any one Treatment Group for 12-month Pooled Data

| [illegible] | Brimonidine Purite 0.15% N=380 | Brimonidine Purite 0.2% N=383 | ALPHAGAN N=383 |
|---|---|---|---|
| Accidental Injury | 9 (2.4%) | 12 (3.1%) | 10 (2.6%) |
| Allergic Conjunctivitis | 36 (9.5%) | 61 (15.9%) | 62 (16.2%) |
| Allergic reaction | 5 (1.3%) | 4 (1.0%) | 7 (1.8%) |
| Arm Pain | 4 (1.1%) | 2 (0.5%) | 4 (1.0%) |
| Arthralgia | 0 | 5 (1.3%) | 1 (0.3%) |
| Arthritis | 11 (2.9%) | 10 (2.6%) | 8 (2.1%) |
| Asthenia | 8 (2.1%) | 6 (2.3%) | 19 (5.0%) |
| Asthenopia | 1 (0.3%) | 5 (1.3%) | 7 (1.8%) |
| Asthma | 5 (1.3%) | 4 (1.0%) | 1 (0.3%) |
| Back Pain | 6 (1.6%) | 11 (2.9%) | 6 (1.6%) |
| Blepharitis | 14 (3.7%) | 5 (1.3%) | 11 (2.9%) |
| Bone Fracture; Cause Unknown | 4 (1.1%) | 2 (0.5%) | 4 (1.0%) |
| Bronchitis | 10 (2.6%) | 5 (1.3%) | 5 (1.3%) |
| Burning sensation in eye | 23 (6.1%) | 30 (7.8%) | 38 (9.9%) |
| Cataract (NOS) | 5 (1.3%) | 8 (2.1%) | 5 (1.3%) |
| Chalazion | 2 (0.5%) | 6 (1.6%) | 0 |
| Chest Pain | 0 | 1 (0.3%) | 4 (1.0%) |
| Conjunctival edema | 6 (1.6%) | 5 (1.3%) | 7 (1.8%) |
| Conjunctival folliculosis | 23 (6.1%) | 30 (7.8%) | 31 (8.1%) |
| Conjunctival hemorrhage | 6 (1.6%) | 3 (0.8%) | 5 (1.3%) |
| Conjunctival hyperemia | 80 (21.1%) | 86 (22.5%) | 105 (27.4%) |
| Conjunctivitis | 4 (1.1%) | 6 (1.6%) | 4 (1.0%) |
| Contact dermatitis | 1 (0.3%) | 0 | 4 (1.0%) |
| Cough increased | 6 (1.6%) | 3 (0.8%) | 6 (1.6%) |
| Cystitis | 2 (0.5%) | 1 (0.3%) | 6 (1.6%) |
| Depression | 3 (0.8%) | 3 (0.8%) | 6 (1.6%) |
| Dermatitis | 3 (0.8%) | 6 (1.6%) | 6 (1.6%) |
| Diabetes Mellitus | 6 (1.6%) | 4 (1.0%) | 4 (1.0%) |
| Diarrhea | 3 (0.8%) | 2 (0.5%) | 4 (1.0%) |
| Dizziness | 4 (1.1%) | 11 (2.9%) | 11 (2.9%) |
| Dyspepsia | 10 (2.6%) | 8 (2.1%) | 5 (1.3%) |
| Dypsnea | 4 (1.1%) | 1 (0.3%) | 4 (1.0%) |
| Epiphora | 16 (4.2%) | 21 (5.5%) | 23 (6.0%) |
| Eye discharge | 9 (2.4%) | 6 (1.6%) | 10 (2.6%) |
| Eye dryness | 15 (3.9%) | 23 (6.0%) | 21 (5.5%) |
| Eye irritation | 7 (1.8%) | 5 (1.3%) | 14 (3.7%) |
| Eye pain | 10 (2.6%) | 17 (4.4%) | 20 (5.2%) |
| Eye pruritus | 35 (9.2%) | 49 (12.8%) | 51 (13.3%) |

| [illegible] | [illegible] | Brimonidine Purite 0.2% N=383 | ALPHAGAN N=383 |
|---|---|---|---|
| Eyelid | 5 (1.3%) | 3 (0.8%) | 6 (1.6%) |
| Eyelid edema | 8 (2.1%) | 15 (3.9%) | 11 (2.9%) |
| Eyelid erythema | 6 (1.6%) | 10 (2.6%) | 12 (3.1%) |
| Face edema | 0 | 4 (1.0%) | 0 |
| Flu syndrome | 11 (2.9%) | 6 (1.6%) | 18 (4.7%) |
| Follicular conjunctivitis | 5 (1.3%) | 3 (0.8%) | 3 (0.8%) |
| Foreign body sensation | 15 (3.9%) | 16 (4.2%) | 23 (6.0%) |
| Headache | 13 (3.4%) | 15 (3.9%) | 10 (2.6%) |
| Hordeolum | 4 (1.1%) | 0 | 1 (0.3%) |
| Hypercholesterolemia | 2 (0.5%) | 4 (1.0%) | 6 (1.6%) |
| Hypertension | 19 (5.0%) | 19 (5.0%) | 18 (4.7%) |
| Infection | 30 (7.9%) | 15 (3.9%) | 27 (7.0%) |
| Infection sinus | 12 (3.2%) | 5 (1.3%) | 4 (1.0%) |
| Insomnia | 3 (0.8%) | 5 (1.3%) | 2 (0.5%) |
| Intraocular Pressure | 2 (0.5%) | 4 (1.0%) | 8 (2.1%) |
| Migraine | 1 (0.3%) | 4 (1.0%) | 1 (0.3%) |
| Nausea | 2 (0.5%) | 2 (0.5%) | 6 (1.6%) |
| Neck Pain | 4 (1.1%) | 0 | 1 (0.3%) |
| Oral dryness | 20 (5.3%) | 37 (9.7%) | 41 (10.7%) |
| Papillary hypertrophy | 3 (0.8%) | 8 (2.1%) | 5 (1.3%) |
| Peridontal abscess | 5 (1.3%) | 3 (0.8%) | 3 (0.8%) |
| Pharyngitis | 10 (2.6%) | 7 (1.8%) | 3 (0.8%) |
| Photophobia | 7 (1.8%) | 1 (0.3%) | 4 (1.0%) |
| Pneumonia | 4 (1.1%) | 2 (0.5%) | 3 (0.8%) |
| Prostatic Disorder | 6 (1.6%) | 2 (0.5%) | 0 (0.0%) |
| Rash | 4 (1.1%) | 7 (1.8%) | 4 (1.8%) |
| Rhinitis | 9 (2.4%) | 6 (1.6%) | 10 (2.6%) |
| Sinusitis | 4 (1.1%) | 1 (0.3%) | 1 (0.3%) |
| Somnolence | 3 (0.8%) | 13 (3.4%) | 11 (2.9%) |
| Stinging sensation in eye | 7 (1.8%) | 1 (0.3%) | 7 (1.8%) |
| Superficial Punctate Keratopathy | 7 (1.8%) | 2 (0.5%) | 4 (1.0%) |
| Tenosynovitis | 5 (1.3%) | 3 (0.8%) | 3 (0.8%) |
| Urinary Tract Infection | 3 (0.8%) | 5 (1.3%) | 8 (2.1%) |
| Visual acuity worsened | 12 (3.2%) | 9 (2.3%) | 9 (2.3%) |
| Visual disturbance | 30 (7.9%) | 40 (10.4%) | 34 (8.9%) |
| Visual field defect | 4 (1.1%) | 9 (2.3%) | 2 (0.5%) |
| Vitreous detachment | 0 | 4 (1.0%) | 0 |
| Vitreous floaters | 6 (1.6%) | 6 (1.6%) | 4 (1.0%) |

**Reviewer's Comments:**

*The Brimonidine-Purite 0.15% 12-month incidence rates for conjunctival hyperemia, eye pruritus, allergic conjunctivitis, epiphora and hypertension show a significant increase over the rates reported in the 3-month studies. This is not unexpected due to the longer duration of exposure to the study drug and previous experience with Alphagan.*

*Allergic conjunctivitis which contributes to a high rate of patient dissatisfaction and discontinued use occurred less frequently in the BP-0.15% group than the BP-0.2% or Alphagan group. (Table 1)*

*There are several adverse events included in this report which were seen in none or ≤ 1% of the subjects during the 3-month trial period. These include asthma, bronchitis, conjunctival hemorrhage, dyspepsia, dyspnea, rhinitis, sinusitis, superficial punctate keratopathy, visual field defect and vitreous floaters. All events are reported in less than 3% of the study population.*

*Two deaths, previously unreported, occurred during this reporting period. Subject 2972-U22 was a 76 year old female who died due to complications from a myocardial infarction and cardiac surgery. Subject 2122-T22 was a 74 year old woman who died from a cardiac arrest.*

**Reviewer's Conclusions**

1) *Information contained in this safety update shows an increase in incidence of several AE's compared to previous safety information reviewed for the original NDA.*

2) *Allergic conjunctivitis in seen in significantly less patients with BP-0.15% than with BP-0.2% or Alphagan.*

3) *Original conclusions regarding the safety of Brimonidine-Purite 0.15% for the lowering of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension are not altered.*

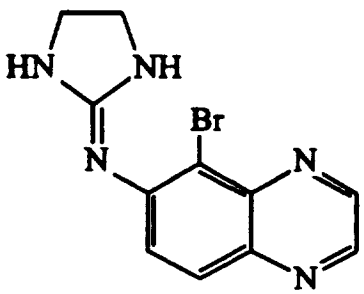
4) *The following events should be included in the labeling: asthma, bronchitis, conjunctival hemorrhage, dyspepsia dyspnea, rhinitis, sinusitis, superficial punctate keratopathy, visual field defect and vitreous floaters.*

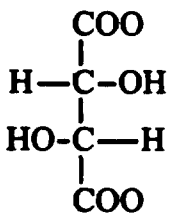
Jennifer D. Harris, M.D.
Medical Officer

NDA 21-262
HFD-550/Div Files
HFD-550/MO/Harris
HFD-550/SMO/Chambers
HFD-550/Acting Div Dir/Bull
HFD-880/Biopharm/Tandon
HFD-725/Biostats/Li
HFD-550/Chem/Rodriquez
HFD-550/PharmTox/Murkerje
HFD-550/PM/Gorski
HFD-340/Carreras

**Medical Officer's Review of NDA 21-262**
Original

| | |
|---|---|
| **NDA 21-262**<br>Medical Officer's Review | **Submission Date:** June 29, 2000<br>**Receipt Date:** June 30, 2000<br>**Review Date:** October 13, 2000 |
| **Proposed Tradename:** | Alphagan-P |
| **Drug:** | Brimonidine-Purite™ Ophthalmic Solution 0.15% |
| **Chemical Name:** | 5-bromo-6-(2-imidazolidinylideneamino) quinoxaline L-tartrate |




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

| | |
|---|---|
| **Sponsor:** | Allergan<br>2525 Dupont Drive<br>P.O. Box 19534<br>Irvine, California 92623-9534 |
| **Pharmacologic Category:** | Alpha 2-agonist |
| **Proposed Indication:** | Reduction of intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension |
| **Dosage Form and Route of Administration:** | Ophthalmic suspension for topical ocular administration |

**NDA Drug Classificaton:** 3S

**Related INDs:** [redacted] Alphagan (AGN 190342-LF)

**Related NDAs:** NDA 20-613 Alphagan (AGN 190342-LF)

**2 Table of Contents** **Page**


| | | | |
|---|---|---|---|
| 3 | Material Reviewed | | 2 |
| 4 | Chemistry/Manufacturing Controls | | 2 |
| 5 | Animal Pharmacology/Toxicology | | 5 |
| 6 | Clinical Background | | 5 |
| 7 | Clinical Sources | | 7 |
| 8 | Clinical Studies | | 8 |
| 8.1 | Study #1 | Protocol 190342-005 | 8 |
| 8.2 | Study #2 | Protocol 190342-007 | 20 |
| 8.3 | Study #3 | Protocol 190342-008 | 41 |
| 9 | Summary of Efficacy and Safety | | 57 |
| 10 | Labeling Review | | 57 |
| 11 | Conclusions | | 63 |
| 12 | Recommendations | | 63 |


## 3 Material Reviewed

NDA 21-262 Volumes 1.1, 1.34-1.97

## 4 Chemistry/Manufacturing Controls – See Chemistry Review

**Table 1 – Quantitative Composition**

| | | | |
|---|---|---|---|
| Brimonidine Tartrate | 0.15 | 1.5 | |
| Purite™ | 0.005 | 0.05 | |
| Sodium Carboxymethylcellulose USP | | | |
| Boric Acid NF | | | |
| Sodium Borate | | | |
| Sodium Chloride USP | | | |
| Potassium Chloride USP | | | |
| Calcium Chloride | | | |
| Magnesium Chloride Hexahydrate USP | | | |
| Hydrochloric Acid NF or Sodium Hydroxide NF | | | |
| Purified Water USP | | | |

a The brimonidine tartrate quantity is corrected for "as is" purity.
b The Purite™ quantity is corrected for raw material assay.
c The sodium carboxymethylcellulose quantity is corrected for moisture content based on the loss-on-drying (LOD) assay

**1 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.**

5 **Animal Pharmacology/Toxicology** – See Pharmacology Review

6 **Clinical Background**

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 pathoetiology 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 decreases IOP. Brimonidine tartrate at a concentration of 0.2% was approved by the United States FDA on September 6, 1996, and is commercially available as ALPHAGAN ® 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.

Concerns have been raised regarding the role of preservatives such as benzalkonium chloride (BAK), which is contained in ALPHAGAN, in producing ophthalmologic allergic reactions and cytotoxicity. Therefore, a new formulation of brimonidine tartrate containing Purite as the preservative was developed. Purite is believed to confer better tolerance as compared with BAK.

Two 1-month, dose-response studies were conducted in humans to evaluate the efficacy and safety of Brimonidine-Purite 0.1% and 0.2%, dosed either BID or TID, compared with ALPHAGAN, Timoptic, and vehicle. Based on the results of 2 phase 2 clinical studies evaluating Brimonidine-Purite 0.1% and 0.2%, Brimonidine-Purite 0.1% was found to be slightly less effective than Brimonidine-Purite 0.2%, ALPHGAN, or Timoptic. Therefore, the 0.15% and 0.2% concentrations were selected for evaluation in phase 3 studies.

6.1 **Relavant Human Experience**

ALPHAGAN® (brimonidine tartrate ophthalmic solution) 0.2% is approved in the United States for the reduction of elevated intraocular pressure in patients with open-angle glaucoma and ocular hypertension. Purite™ is used as a preservative in 2 currently marketed over-the-counter preparations, REFRESH TEARS® and LENS PLUS® Purite™ Saline.

**Reviewer's Comments:**
*Refresh Tears and Lens Plus Purite were not subjects of prior approval applications to the FDA.*

**6.2 Foreign Experience**

Brimonidine-Purite™ has not been marketed in any country. However, the active ingredient, brimonidine tartrate, with benzalkonium chloride as the preservative (BAK) is marketed as ALPHAGAN® 0.2% in several countries.

**6.3 Human Pharmacology, Pharmacokinetics, & Pharmacodynamics –** See Biopharmacology Review

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

## 7 Description of Clinical Data Sources

| Protocol Type | Study Design | Duration | Population | Treatment Groups | Dosing | Gender/Race | Enrolled/Completed |
|---|---|---|---|---|---|---|---|
| 190342-005 Phase 2 Safety and Efficacy | Multicenter, randomized, investigator masked, vehicle controlled | 1 month | Open angle glaucoma and ocular hypertension | Brimonidine Purite 0.1%<br>Brimonidine Purite 0.2%<br>Timoptic 0.5% | 1gtt BID | 59M/63F<br>94 white<br>15 black<br>13 hispanic | 122/120 |
| 190342-007 phase 3 Safety and Efficacy | Multicenter, randomized, double masked, active control | 3 months | Open angle glaucoma and ocular hypertension | Brimonidine Purite 0.15%<br>Brimonidine Purite 0.2%<br>Alphagan | 1gtt TID | 260M/333F<br>439 white<br>97 black<br>51 hispanic<br>4 asian<br>2 other | 593/519 |
| 190342-008 phase 3 Safety and Efficacy | Multicenter, randomized, double masked, active control | 3 months | Open angle glaucoma and ocular hypertension | Brimonidine Purite 0.15%<br>Brimonidine Purite 0.2%<br>Alphagan | 1gtt TID | 238M/316F<br>467 white<br>57 black<br>26 hispanic<br>2 asian<br>2 other | 554/483 |

## 8 Clinical Studies

### 8.1 Study #1 Protocol 190342-005

Title: A multicenter, investigator-masked, randomized, vehicle-controlled, parallel, one month study of the safety, efficacy, and acceptability of twice-daily-dosed 0.1% and 0.2% Brimonidine-purite compared with [redacted] Timoptic 0.5% in patients with glaucoma or ocular hypertension

Objective: To evaluate the safety, efficacy and acceptability of 0.1% and 0.2% Brimonidine-Purite compared with [redacted] Timoptic 0.5% administered twice daily for one month in patients with glaucoma or ocular hypertension to determine the diurnal intraocular pressure (IOP) effects of 0.1% and 0.2% Brimonidine-Purite.

Study Design: This study was a multi-center, randomized, investigator-masked, parallel comparison consisting of 6 scheduled visits. Patients with glaucoma or OHT were randomly assigned to 1of the 4 treatment groups: Brimonidine-Purite 0.1%, Brimonidine-Purite 0.2%, [redacted] or Timoptic 0.5%. Patients were instructed to instill 1 drop of study medication in each eye twice daily for 1 month.

Test Drug Schedule: One drop administered in each eye twice daily for 1 month

**Reviewers Comments:**
*This trial was designed as investigator masked. This makes the safety data difficult to interpret adequately secondary to patient bias. Additionally the efficacy results may be unreliable since patients may have unmasked their treatment to the investigators.*

APPEARS THIS WAY
ON ORIGINAL

**Table 3 - Clinical Sites – Study 005**

| Principal Investigator Name (Number), Address | Number of Subjects Enrolled | Subject ID Numbers |
|---|---|---|
| Mark Abelson, M.D. (1584)<br>863 turnpike Street, Suite 224<br>North Andover, MA 01845 | 20 | 301-320 |
| Tom Mundorf, M.D. (1485)<br>Presbyterian Medical tower<br>1718 E. 4th Street, Suite 902<br>Charlotte, NC 28204 | 27 | 401-427 |
| Howard Schenker, M.D. (2429)<br>2100 Clinton Ave., South<br>Rochester, NY 14618 | 13 | 501-513 |
| Steven Simmons, M.D. (1655)<br>The Center for Sight<br>349 Northern Blvd.<br>Albany, NY 12204 | 18 | 101-118 |
| Tom Walters, M.D. (1634)<br>1700 South Mopac<br>Austin, TX 78746 | 44 | 201-244 |

**Reviewer's Comments:**
*The agency prefers patients to be randomized with at least ten patients per arm per center in multicenter trials so that interaction between centers can be evaluated.*

**Selection of Study Population**

**Inclusion Criteria**

The following were requirements for patient entry into the study:

- Male or female, 21years of age or older
- Glaucoma (including primary open-angle, pseudoexfoliative, pigment dispersion, chronic angle-closure with a patent peripheral iridectomy/iridotomy for at least 3 months) or OHT in each eye

- Likely to be controlled on monotherapy
- Baseline (day 0) hour 0 IOP of ≥ 23 mm Hg and ≤ 34 mm Hg in each eye and asymmetry of IOP not greater than 5 mm Hg
- Best-corrected visual acuity of 20/80 or better in each eye
- Informed consent was obtained
- Able to follow study instructions and likely to complete all required visits
- For women of childbearing potential (a woman was considered of childbearing potential unless she was postmenopausal, had her uterus and/or both ovaries removed, or had a bilateral tubal ligation) a negative pregnancy test result was required at baseline (day 0)
- Ability to potentially go without anti-glaucoma medications for up to 8 weeks (includes 4-week washout period) without significant risk to the patient

**Exclusion Criteria**

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

- Uncontrolled systemic disease
- Severe cardiovascular disease
- Women who were pregnant, nursing, or planning a pregnancy or who were of childbearing potential (a woman is considered of childbearing potential unless she is postmenopausal, has had her uterus and/or both ovaries removed, or has had a bilateral tubal ligation) and not using a reliable form of contraception
- Patients with depression, cerebral or active coronary insufficiency or orthostatic hypotension
- Abnormally low or high blood pressure or heart rate for age
- Known allergy or sensitivity to any of the study medication ingredients
- Contraindications to brimonidine therapy such as concurrent use of monoamine oxidase (MAO) inhibitor therapy
- Contraindications to beta-adrenoceptor antagonist therapy such as obstructive pulmonary disease, bronchial asthma, heart block more severe than first degree or uncontrolled congestive heart failure

- Anticipated alteration of existing chronic therapy with agents which could have had a substantial effect on IOP, including, but not necessarily limited to systemic adrenergic agents including beta-adrenergic blocking agents (e.g., propanolol, metoprolol, nadolol, timolol, atenolol)

- Anticipated treatment with adrenergic-augmenting psychotropic drugs (e.g., desipramine, amitriptyline)

- Any other active ocular disease (e.g., uveitis, ocular infections, or severe dry eye). However, patients with chronic mild blepharitis, cataract, age-related macular degeneration, or background diabetic retinopathy could have been enrolled at the discretion of the investigator

- Corneal abnormalities that would preclude accurate readings with an applanation tonometer

- Anticipated wearing of contact lenses during the study

- Any glaucoma other than those listed in the inclusion criteria

- Required chronic use of other ocular medications during the study (Intermittent use of artificial tear product was allowed)

- Laser or any other ocular surgery within the three months prior to entry or intraocular filtering surgery in the past

- Visual field loss which in the opinion of the investigator was functionally significant

- Participation in a drug or device research study within 30 days prior to entry into this study or concurrent participation in any other drug or device research study

- 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 the patient's participation in the study

- Patients must have been appropriately washed-out of their anti-glaucoma medications within the washout periods listed in the protocol

**Study Medications**

Brimonidine-Purite 0.2% ophthalmic solution (Allergan formulation number 9115X, lot number 11209)

[redacted]

Brimonidine-Purite 0.1% ophthalmic solution (Allergan formulation number 9118X, lot number 11208)

[redacted]

[redacted]

Timoptic - timolol maleate 0.5% ophthalmic solution (Allergan Formulation Number 6151X, lot numbers 11210 and 11262) Contains timolol 0.5% and benzalkonium chloride 0.01%, with purified water, monobasic and dibasic sodium phosphate, and sodium hydroxide to adjust pH.

**Study Masking**

The investigational materials were packaged, labeled, and masked by Allergan in a manner consistent with the study design. They were coded at Allergan using a computer-generated randomization list. Study medications were provided in identical masked bottles. The study number and patient number were identified on the label of the medication box. The medication was identified as an investigational compound, for external use only. The investigator was unaware of the patient's study medication.

**Reviewer's Comments:** *This study was not double-masked. It was only masked to the investigator.*

**Efficacy Variables**

Intraocular pressure was measured using the [redacted] This was measured at prestudy and at all subsequent visits during the treatment period. Within each active treatment group, a mean decrease of 3 mm Hg in IOP from baseline and of at least 2 mm Hg greater than that achieved by vehicle was considered clinically significant.

**Reviewers Comments:**
*The agency does not accept the above criteria as demonstrating efficacy. Efficacy would be demonstrated by showing equivalence to timolol 0.5% or the ability of the drug to demonstrate at least a 25% reduction from baseline at the time of peak effect and at least 20% reduction from baseline at the time of trough effect.*

**Table 4 - Schedule of Visits and Measurements - Study 005**

| [illegible] | [illegible] | [illegible] | [illegible] | [illegible] | [illegible] | [illegible] | [illegible] | [illegible] | [illegible] |
|---|---|---|---|---|---|---|---|---|---|
| 1 (prestudy) | 0 | X | | X | X | X | X | X | |
| **Washout-Period (2-30) Days** | | | | | | | | | |
| 2 (Day 0 – Baseline) | 0 | | x | X | X | X | | | |
| | 1 | | | X | | | | | |
| | 2 | | | X | | | | | |
| | 3 | | | X | | | | | |
| | 5 | | | X | | | | | |
| | 7 | | | X | | | | | |
| | 9 | | | X | | | | | |
| | 12 | | | X | | | | | |
| 3 (Day 1) | 0 | | | X | X | X | | | |
| **Dosing Begins Following Hour 0 Examination** | | | | | | | | | |
| | 1 | | | X | | X | | | X |
| | 2 | | | X | | | | | |
| 4 (Day 7) | 0 | | | X | X | X | | | X |
| | 1 | | | X | | | | | |
| | 2 | | | X | | | | | |
| 5 (Day 21) | 0 | | | X | X | X | | | X |
| | 1 | | | X | | | | | |
| | 2 | | | X | | | | | |
| | 3 | | | X | | | | | |
| | 5 | | | X | | | | | |
| | 7 | | | X | | | | | |
| | 9 | | | X | | | | | |
| | 12 | | | X | | | | | |
| 6 (Day 28) | 0 | | | X | X | X | | | X |
| | 1 | | | X | | X | | | X |
| | 2 | | | X | | | | | |
| | 3 | | | X | | | | | |
| | 5 | | | X | | | | | |
| | 7 | | | X | | | | | |
| | 9 | | | X | | | | | |
| | 12 | | | X | | | X* | | |

Key to Abbreviations
IOP = Intraocular Pressure
HR = Hear Rate – seated, resting for at least 5 minutes
BP = Blood Pressure – seated, resting for at least 5 minutes
BIO = Biomicroscopy – undilated pupil
OPH = Ophthalmoscopy
VA = Visual Acuity (ETDRS chart)
VF = Visual Field Examination (visual fields collected up to six months prior to baseline visit will be accepted
* = Ophthalmoscopy should be performed after Hour 12 IOP measurement

**Reviewer's Comments:**

*The washout period for all drugs was in accordance with agency recommendations, however the study duration is shorter than recommended to establish efficacy or safety.*

**Subject Disposition and Demographics**

**Disposition**

Of the 122 patients enrolled, 30 were in the Brimonidine-Purite 0.1% group, 30 in the Brimonidine-Purite 0.2% group, 31 in the Timoptic group, and 31 in the vehicle group. For patients enrolled, the completion rate was 93% for Brimonidine-Purite 0.1% and 100% for Brimonidine-Purite TM 0.2%, Timoptic and Vehicle. No patients were excluded from the per-protocol analysis. Two patients discontinued and exited from the study.



**Table 5 – Discontinued Patients and Reason – Study 005**

| Patient | Treatment | Reason |
|---|---|---|
| 1634-244 | Brimonidine-Purite 0.1% | Lack of efficacy |
| 2429-504 | Brimonidine-Purite 0.1% | Personal reasons |



APPEARS THIS WAY
ON ORIGINAL