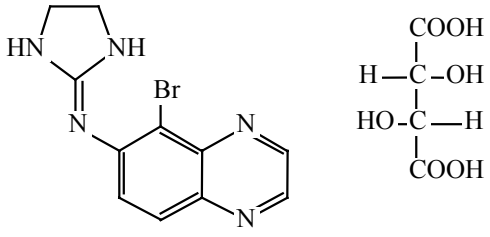
ALPHAGAN®
(brimonidine tartrate ophthalmic solution) 0.5%

Sterile

DESCRIPTION

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



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

CAS Number: 59803-98-4

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

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

CLINICAL PHARMACOLOGY
Mechanism of action:

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

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

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

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

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

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

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

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

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

PRECAUTIONS
General:

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Nursing Mothers:
It is not known whether this drug is excreted in human milk; in animal studies brimonidine tartrate was excreted in breast milk. A decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

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

The safety and effectiveness of **ALPHAGAN®** have not been studied in pediatric patients below the age of 2 years. **ALPHAGAN®** is not recommended for use in pediatric patients under the age of 2 years.

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

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

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

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

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

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

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

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

Rx only

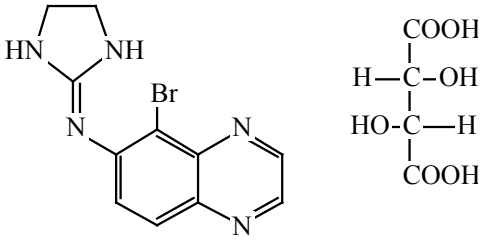
US Patent 6,194,415
Revised December 2001
7831X

ALPHAGAN®
(brimonidine tartrate ophthalmic solution) 0.2%

Sterile

DESCRIPTION

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



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

CAS Number 59803-98-4

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

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

CLINICAL PHARMACOLOGY

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Pregnancy: Teratogenic Effects: Pregnancy Category B

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

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

Nursing Mothers:
It is not known whether this drug is excreted in human milk; in animal studies brimonidine tartrate was excreted in breast milk. A decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

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

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

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

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

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

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

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

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

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

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

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

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

Rx only

® ALLERGAN

Irvine, CA 92612

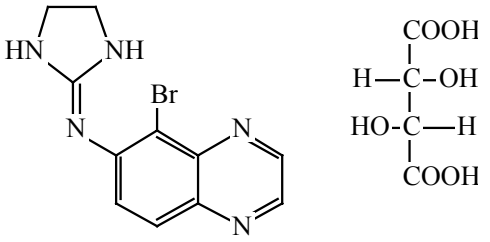
US Patent 6,194,415
Revised December 2001
7831X

ALPHAGAN® P
(brimonidine tartrate ophthalmic solution) 0.15%

Sterile

DESCRIPTION

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



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

CAS Number: 59803-98-4

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

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

CLINICAL PHARMACOLOGY

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Nursing Mothers:
It is not known whether this drug is excreted in human milk; in animal studies brimonidine tartrate was excreted in breast milk. A decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

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

The safety and effectiveness of brimonidine tartrate ophthalmic solution have not been studied in pediatric patients below the age of 2 years. Brimonidine tartrate ophthalmic solution is not recommended for use in pediatric patients under the age of 2 years. (Also refer to Adverse Reactions section.)

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

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

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

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

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

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

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

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

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

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

HOW SUPPLIED

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

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

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

Rx Only

® ALLERGAN

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

Reviewer's Comments:

Acceptable.

Recommended Regulatory Action:

The above proposed labels are recommended for approval.

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

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

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/s/

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

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