

NDA 20490/S-008

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HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ALPHAGAN® 0.5% safely and effectively. See full prescribing information for ALPHAGAN® 0.5%.

ALPHAGAN® (brimonidine tartrate ophthalmic solution) 0.5%

For Topical Ophthalmic Use

Initial U.S. Approval: 1996

INDICATIONS AND USAGE

ALPHAGAN® 0.5% is an alpha-adrenergic agonist indicated for the prevention of post-operative intraocular pressure (IOP) elevations in patients undergoing argon laser trabeculoplasty (ALT). (1)

DOSAGE AND ADMINISTRATION

One drop of ALPHAGAN® 0.5% in the operative eye 30-45 minutes before ALT surgery and immediately following ALT surgery. (2)

DOSAGE FORMS AND STRENGTHS

Solution containing 5 mg/mL brimonidine tartrate. (3)

CONTRAINDICATIONS

Neonates and infants (under the age of 2 years). (4.1)

WARNINGS AND PRECAUTIONS

Potential of vascular insufficiency. (5.1)

ADVERSE REACTIONS

- Most common adverse reactions reported in conjunction with ALT: transient conjunctival blanching (50%) and upper lid retraction (30%). (6.1)
- Adverse reactions reported in 1% to 4% of the patients: drowsiness/tiredness, dizziness, corneal edema, and ocular irritation (encompassing foreign body sensation, ocular pain and discomfort). (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Allergan at 1-800-433-8871 or the FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Antihypertensives/cardiac glycosides may lower blood pressure. (7.1)
- Use with CNS depressants may result in an additive or potentiating effect. (7.2)
- Tricyclic antidepressants may potentially blunt the hypotensive effect of systemic clonidine. (7.3)
- Monoamine oxidase inhibitors may result in increased hypotension. (7.4)

USE IN SPECIFIC POPULATIONS

Use with caution in children $\geq$ 2 years of age. (8.4)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 3/2016

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*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

ALPHAGAN[®] (brimonidine tartrate ophthalmic solution) 0.5% is indicated for the prevention of post-operative IOP elevations in patients undergoing argon laser trabeculoplasty (ALT).

2 DOSAGE AND ADMINISTRATION

The recommended dose is one drop of **ALPHAGAN**[®] 0.5% in the operative eye 30-45 minutes before ALT surgery and immediately following ALT surgery.

3 DOSAGE FORMS AND STRENGTHS

Solution containing 5 mg/mL brimonidine tartrate.

4 CONTRAINDICATIONS

4.1 Neonates and Infants (under the age of 2 years)

ALPHAGAN[®] is contraindicated in neonates and infants (under the age of 2 years) [*see Use in Specific Populations (8.4)*].

4.2 Hypersensitivity Reactions

ALPHAGAN[®] is contraindicated in patients who have exhibited a hypersensitivity reaction to any component of this medication in the past [*see Adverse Reactions (6.1) and (6.2)*].

5 WARNINGS AND PRECAUTIONS

5.1 Potentiation of Vascular Insufficiency

ALPHAGAN[®] may potentiate syndromes associated with vascular insufficiency. **ALPHAGAN**[®] should be used with caution in patients with depression, cerebral or coronary insufficiency, Raynaud's phenomenon, orthostatic hypotension, or thromboangiitis obliterans.

5.2 Severe Cardiovascular Disease

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.

6 ADVERSE REACTIONS

The following serious adverse reactions are described elsewhere in the labeling:

- Potentiation of Vascular Insufficiency [*see Warnings and Precautions (5.1)*]
- Severe Cardiovascular Disease [*see Warnings and Precautions (5.2)*]
- Neonates and Infants (under the age of 2 years) [*see Contraindications (4.1)*]

6.1 Clinical Studies Experience

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

- The most common adverse reactions reported in association with the use of **ALPHAGAN**® 0.5% in conjunction with ALT: transient conjunctival blanching in 50% of patients and upper lid retraction in 30% of patients.
- The adverse reactions reported in 1% to 4% of the patients: drowsiness/tiredness, dizziness, corneal edema, and ocular irritation (encompassing foreign body sensation, ocular pain and discomfort).
- The adverse reactions occurring in approximately 10-20% of the subjects receiving brimonidine ophthalmic solution (0.1-0.2%): allergic conjunctivitis, conjunctival hyperemia, and eye pruritus.
- The adverse reactions occurring in approximately 5-9% of patients: burning sensation, conjunctival folliculosis, hypertension, ocular allergic reaction, and visual disturbance.
- The adverse reactions occurring in approximately 1-4% of the subjects receiving brimonidine ophthalmic solution (0.1-0.2%): abnormal taste, allergic reaction, asthenia, blepharitis, blepharoconjunctivitis, blurred vision, bronchitis, cataract, conjunctival edema, conjunctival hemorrhage, conjunctivitis, cough, dyspepsia, dyspnea, epiphora, eye discharge, eye dryness, eye irritation, eye pain, eyelid edema, eyelid erythema, fatigue, flu syndrome, follicular conjunctivitis, gastrointestinal disorder, headache, hypercholesterolemia, hypotension, infection (primarily colds and respiratory infections), insomnia, keratitis, lid disorder, 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 adverse reactions reported in <1% of subjects: corneal erosion, hordeolum, nasal dryness, taste perversion, browache, dry mouth, and nausea.

6.2 Postmarketing Experience

The following reactions have been identified during postmarketing 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 reactions, 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, hypersensitivity, iritis, keratoconjunctivitis sicca, miosis, nausea, skin reactions (including erythema, eyelid pruritus, rash, and vasodilation), syncope, and tachycardia.
- Apnea, bradycardia, coma, hypotension, hypothermia, hypotonia, lethargy, pallor, respiratory depression, and somnolence in infants receiving brimonidine tartrate ophthalmic solutions.

7 DRUG INTERACTIONS

7.1 Antihypertensives/Cardiac Glycosides

Because **ALPHAGAN**[®] may reduce blood pressure, caution in using drugs such as antihypertensives and/or cardiac glycosides with **ALPHAGAN**[®] is advised.

7.2 CNS Depressants

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.

7.3 Tricyclic Antidepressants

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. Caution is advised in patients taking tricyclic antidepressants which can affect the metabolism and uptake of circulating amines.

7.4 Monoamine Oxidase Inhibitors

Monoamine oxidase (MAO) inhibitors may theoretically interfere with the metabolism of brimonidine and potentially result in an increased systemic side-effect such as hypotension. Caution is advised in patients taking MAO inhibitors which can affect the metabolism and uptake of circulating amines.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B: Teratogenicity studies have been performed in animals.

Brimonidine tartrate was not teratogenic when given orally during gestation days 6 through 15 in rats and days 6 through 18 in rabbits. The highest doses of brimonidine tartrate in rats (2.5 mg/kg/day) and rabbits (5 mg/kg/day) achieved AUC exposure values 600-fold higher or 33-fold higher, respectively, than similar values estimated in humans treated with **ALPHAGAN**[®] 0.5%, one drop in one eye, twice daily.

There are no adequate and well-controlled studies in pregnant women; however, 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.

8.3 Nursing Mothers

It is not known whether **ALPHAGAN**[®] is excreted in human milk, although in animal studies, brimonidine tartrate has been shown to be excreted in breast milk. Because of the potential for serious adverse reactions from **ALPHAGAN**[®] in nursing infants, 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.

8.4 Pediatric Use

ALPHAGAN® is contraindicated in children under the age of 2 years [see CONTRAINDICATIONS, (4.1)]. During postmarketing surveillance, apnea, bradycardia, coma, hypotension, hypothermia, hypotonia, lethargy, pallor, respiratory depression, and somnolence have been reported in infants receiving brimonidine. The safety and effectiveness of brimonidine tartrate have not been studied in children below the age of 2 years.

In a well-controlled clinical study conducted in pediatric glaucoma patients (ages 2 to 7 years) the most commonly observed adverse reactions 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 (greater than 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.

8.5 Geriatric Use

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

8.6 Special Populations

ALPHAGAN® has not been studied in patients with hepatic impairment.

ALPHAGAN® has not been studied in patients with renal impairment. The effect of dialysis on brimonidine pharmacokinetics in patients with renal failure is not known.

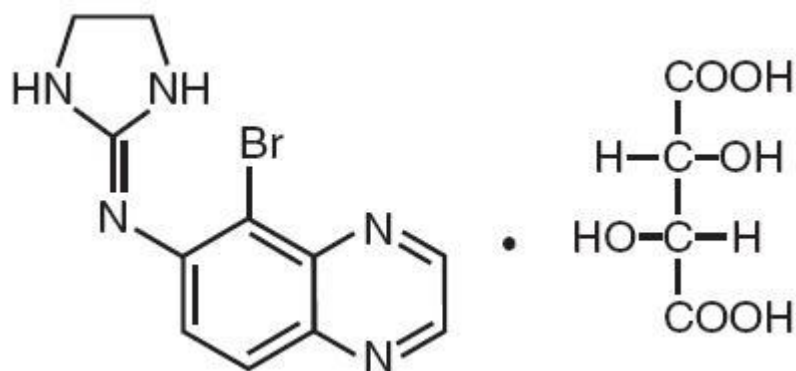
10 OVERDOSAGE

Very limited information exists on accidental ingestion of brimonidine in adults; the only adverse reaction reported to date has been hypotension. Symptoms of brimonidine overdose have been reported in neonates, infants, and children receiving brimonidine tartrate as part of medical treatment of congenital glaucoma or accidental oral ingestion [see *Use in Specific Populations* (8.4)]. Treatment of an oral overdose includes supportive and symptomatic therapy; a patent airway should be maintained.

11 DESCRIPTION

ALPHAGAN® (brimonidine tartrate ophthalmic solution) 0.5%, sterile, is a relatively selective alpha-2 adrenergic receptor agonist for ophthalmic use.

The structural formula of brimonidine tartrate is:



5-Bromo-6-(2-imidazolidinylideneamino) quinoxaline L-tartrate; MW= 442.24

In solution, **ALPHAGAN**[®] (brimonidine tartrate ophthalmic solution) 0.5% has a clear, greenish-yellow color.

Brimonidine tartrate appears as an off-white to pale-yellow powder and is water soluble (34 mg/mL).

Each mL of **ALPHAGAN**[®] solution contains the active ingredient brimonidine tartrate 0.5% (5 mg/mL) with the inactive ingredients polyvinyl alcohol; sodium chloride; sodium citrate; citric acid; benzalkonium chloride 0.005% (0.05 mg/mL) as a preservative; purified water; and hydrochloric acid and/or sodium hydroxide to adjust pH (6.3-6.5).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

ALPHAGAN[®] 0.5% is an alpha adrenergic receptor agonist with 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.

12.3 Pharmacokinetics

Absorption

After ocular administration of a 0.5% solution, plasma concentrations peaked within 1 to 4 hours (approximately 0.1 ng/mL) and declined with a systemic half-life of approximately 3 hours.

Distribution

The protein binding of brimonidine has not been studied.

Metabolism

In humans, brimonidine is extensively metabolized by the liver.

Excretion

Urinary excretion is the major route of elimination of brimonidine and its metabolites. Approximately 87% of an orally-administered radioactive dose of brimonidine was eliminated within 120 hours, with 74% found in the urine.

13 NONCLINICAL TOXICOLOGY

13.1 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 mg/kg/day in rats achieved approximately 250 and 200 times, respectively, the plasma C_{max} drug concentration in humans treated with one drop of **ALPHAGAN**[®] 0.5% into one eye twice daily, the recommended ophthalmic dose.

Brimonidine tartrate was not mutagenic or clastogenic in a series of *in vitro* and *in vivo* studies including the Ames bacterial reversion test, a chromosomal aberration assay in Chinese Hamster Ovary (CHO) cells, and three *in vivo* studies in CD-1 mice: a host-mediated assay, cytogenic study and dominant lethal assay.

A reproduction and fertility study in rats with brimonidine tartrate demonstrated no adverse effect on male or female fertility at oral doses up to 1 mg/kg, estimated as approximately 200 times the systemic exposure (AUC) following the maximum recommended human ophthalmic dose of **ALPHAGAN**[®] 0.5%.

14 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% 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**[®] 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**[®] eyes compared with 40% of vehicle-treated eyes.

Incidence (%) of IOP Elevations ≥ 10 mm Hg Following Argon Laser Trabeculoplasty (360° of angle treated) When **ALPHAGAN**[®] 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

16 HOW SUPPLIED/STORAGE AND HANDLING

ALPHAGAN[®] (brimonidine tartrate ophthalmic solution) 0.05% is supplied sterile in unit-dose vials containing 0.4 mL each and packaged in cartons as follows:

24 Single-Use Vials 0.4 mL each: NDC 0023-XXXX-24

Storage: Store at or below 25°C (77°F). Properly dispose of unit-dose vial after each single patient use.

17 PATIENT COUNSELING INFORMATION

Handling the Container

Patients should be instructed that ocular solutions, if handled improperly or if the tip of the dispensing container contacts the eye or surrounding structures, can become contaminated by common bacteria known to cause ocular infections. Serious damage to the eye and subsequent loss of vision may result from using contaminated solutions.

When to Seek Physician Advice

Patients should also be advised that if they develop an intercurrent ocular condition (e.g., trauma or infection), have ocular surgery, or develop any ocular reactions, particularly conjunctivitis and eyelid reactions, they should immediately seek their physician's advice concerning the continued use of ALPHAGAN®.

Use with Other Ophthalmic Drugs

If more than one topical ophthalmic drug is being used, the drugs should be administered at least five minutes between applications.

Potential for Decreased Mental Alertness

As with other similar medications, 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.

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