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

----------RECENT MAJOR CHANGES----------

Dosage and Administration (2)	9/2025
Warnings and Precautions (5.3)	9/2025

----------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 in the operative eye 30 to 45 minutes before ALT surgery and immediately following ALT surgery. (2)

----------DOSAGE FORMS AND STRENGTHS----------
Ophthalmic solution containing 0.5% (5 mg/mL) brimonidine tartrate in a single-dose vial. (3)

----------CONTRAINDICATIONS----------
- Neonates and infants (pediatric patients younger than 2 years old). (4.1)
- Hypersensitivity Reactions. (4.2)

----------WARNINGS AND PRECAUTIONS----------
Potentiation 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 AbbVie at 1-800-678-1605 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 IN SPECIFIC POPULATIONS----------
Use with caution in pediatric patients aged 2 years and older. (8.4)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 9/2025

FULL PRESCRIBING INFORMATION: CONTENTS*

*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 to 45 minutes before ALT surgery and immediately following ALT surgery.

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

3 DOSAGE FORMS AND STRENGTHS

Ophthalmic solution containing 0.5% (5 mg/mL) brimonidine tartrate in a single-dose vial.

4 CONTRAINDICATIONS

4.1 Neonates and Infants (Pediatric Patients Younger than 2 Years Old)

ALPHAGAN is contraindicated in neonates and infants (pediatric patients younger than 2 years old) [*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.

5.3 Contamination of Topical Ophthalmic Products After Use

Do not touch the tip of the dispensing container to the eye or surrounding structures. Serious damage to the eye and subsequent loss of vision may result from using contaminated solutions *[see Patient Counseling Information (17)]*.

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)*]
- Contamination of Topical Ophthalmic Products After Use *[see Warnings and Precautions (5.3)]*
- Neonates and Infants (Pediatric Patients Younger than 2 Years Old) [*see Contraindications (4.1)*]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials 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% to 20% of the subjects receiving brimonidine ophthalmic solution (0.1% to 0.2%): allergic conjunctivitis, conjunctival hyperemia, and eye pruritus.
- The adverse reactions occurring in approximately 5% to 9% of patients: burning sensation, conjunctival folliculosis, hypertension, ocular allergic reaction, and visual disturbance.
- The adverse reactions occurring in approximately 1% to 4% of the subjects receiving brimonidine ophthalmic solution (0.1% to 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 less than 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 postapproval use of brimonidine tartrate ophthalmic solutions. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Bradycardia, depression, hypersensitivity, iritis, keratoconjunctivitis sicca, miosis, nausea, skin reactions (including erythema, eyelid pruritus, rash, and vasodilation), syncope, and tachycardia.
- Apnea, 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.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no adequate and well-controlled studies with ALPHAGAN in pregnant women. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

In animal studies, brimonidine crossed the placenta and entered into the fetal circulation to a limited extent *(see Data)*. Because animal reproduction studies are not always predictive of human response, ALPHAGAN should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus.

Data

Human Data

Limited available data from postmarketing safety reports and published literature with topical use of brimonidine ophthalmic solution in pregnant women are insufficient to inform a drug- associated risk of pregnancy-related adverse outcomes including miscarriage, stillbirth, congenital anomaly, and events experienced by offspring while breastfeeding.

Animal Data

Embryofetal studies were conducted in pregnant rabbits administered brimonidine tartrate by daily oral gavage on gestation days 6 to 18, to target the period of organogenesis. Brimonidine caused miscarriage at 5 mg/kg/day (12-fold the recommended human ophthalmic dose [RHOD] based on AUC. The no observed adverse effect level (NOAEL) for developmental toxicity in rabbits was 1 mg/kg/day (2.3-fold the RHOD based on AUC). No treatment-related malformations were observed in rabbits. Signs of maternal sedation and fatigue were observed at all dose levels; the lowest observed adverse effect level (LOAEL) for maternal toxicity was 5 mg/kg/day, based on the dose-response for these signs.

Embryofetal studies were conducted in pregnant rats administered brimonidine tartrate by daily oral gavage on gestation days 6 to 15, to target the period of organogenesis. The NOAEL for developmental toxicity was 2.5 mg/kg/day (236-fold the RHOD based on AUC). No treatment-related malformations were observed in rats. The LOAEL for maternal toxicity was 2.5 mg/kg/day, based on signs of sedation and fatigue. The maternal NOAEL was 1.0 mg/kg/day (71-fold the RHOD based on AUC).

After pregnant rats received a single oral dose of ^{14}C-brimonidine tartrate, brimonidine and metabolites crossed the placenta and were detectable in fetal blood and organs.

8.2 Lactation

Risk Summary

It is not known whether brimonidine tartrate is excreted in human milk. In animal studies, brimonidine tartrate has been shown to cross the blood-brain barrier and is excreted into breast milk after oral administration to lactating rats *(see Data)*. Because of the potential for serious adverse reactions, including central nervous system depression and apnea, from ALPHAGAN in nursing infants, ALPHAGAN is not recommended for use during lactation.

Data

Animal Data

After a single oral dose of ^{14}C-labeled brimonidine tartrate to lactating rats, brimonidine and metabolites were detected in milk. After male and female rats received a single oral dose of ^{14}C-brimonidine tartrate, brimonidine crossed the blood-brain barrier. Radiolabel was detected in the cerebellum, cerebrum, and spinal cord.

8.4 Pediatric Use

ALPHAGAN is contraindicated in pediatric patients younger than 2 years old *[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.

In a well-controlled clinical study conducted in pediatric glaucoma patients aged 2 to 7 years old, the most commonly observed adverse reactions with brimonidine tartrate ophthalmic solution 0.2% dosed three times

daily were somnolence (50% to 83% in pediatric patients aged 2 to 6 years old) and decreased alertness. In pediatric patients 7 years and older (greater than 20 kg), somnolence appears to occur less frequently (25%). Approximately 16% of pediatric patients on brimonidine tartrate ophthalmic solution 0.2% 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.

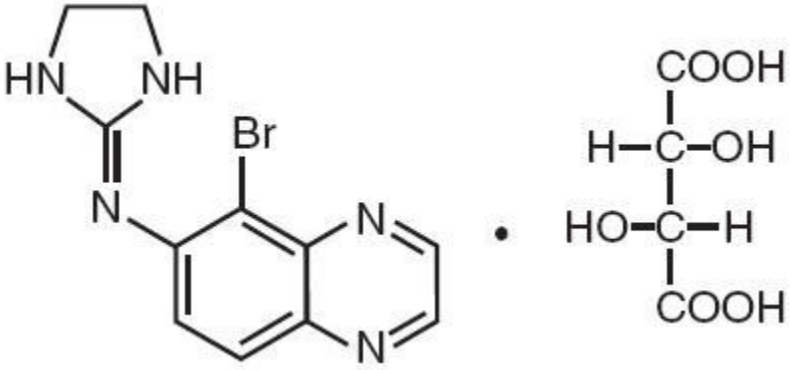
10 OVERDOSAGE

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 topical 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 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
Brimonidine was approximately 29% bound to plasma proteins in healthy subjects.

Elimination
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

Carcinogenesis
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 43 and 35 times, respectively, the recommended human ophthalmic dose (RHOD) based on C_{max}.

Mutagenesis
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, cytogenetic study and dominant lethal assay.

Impairment of Fertility
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 (approximately 71 times the recommended human ophthalmic dose [RHOD] based on estimated AUC).

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 $\geq$ 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 (360º 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) 0.5% is supplied sterile in single-dose vials containing 0.4 mL each and packaged in cartons as follows:

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

Storage: Store at or below 25°C (77°F). Properly dispose of single-dose vial and unused portion after use.

17 PATIENT COUNSELING INFORMATION

Handling the Container

Instruct patients 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

Advise patients 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

Advise patients that 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, advise caution to patients of the potential for a decrease in mental alertness.

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