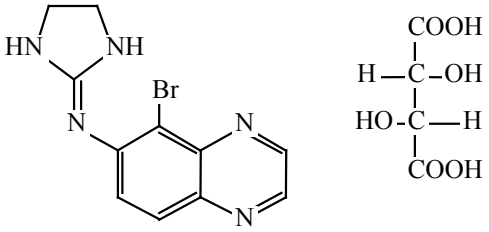
ALPHAGAN®
(brimonidine tartrate ophthalmic solution) 0.5%

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.

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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.

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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**®.

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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.

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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

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