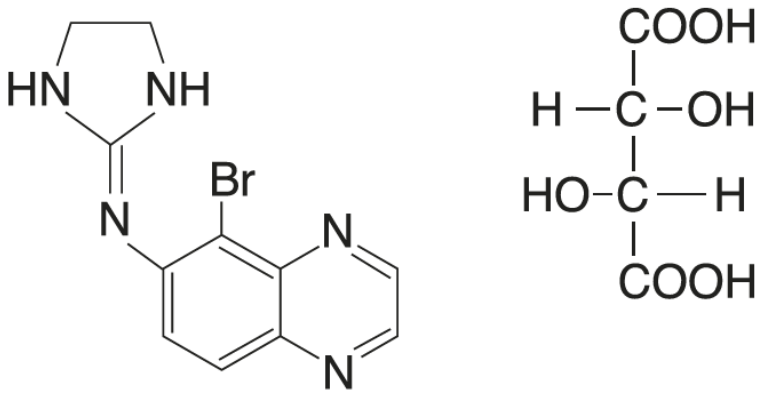
Brimonidine tartrate

ALPHAGAN® P
1.5 mg/mL (0.15%) Sterile Ophthalmic Solution

DESCRIPTION

Brimonidine tartrate ophthalmic solution (ALPHAGAN®P) 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: $C_{11}H_{10}BrN_5 \bullet C_4H_6O_6$
CAS Number: 59803-98-4

In solution, brimonidine tartrate ophthalmic solution (ALPHAGAN®P) 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 brimonidine tartrate ophthalmic solution (ALPHAGAN®P) 0.15% 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:
Brimonidine tartrate ophthalmic solution (ALPHAGAN®P) 0.15% 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 Evaluation:
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 brimonidine tartrate ophthalmic solution (ALPHAGAN®P) 0.15% compared with brimonidine tartrate ophthalmic solution (ALPHAGAN®) 0.2% administered three-times-daily in patients with open-angle glaucoma or ocular hypertension. Those results indicated that brimonidine tartrate ophthalmic solution (ALPHAGAN®P) 0.15% is comparable in IOP lowering effect to brimonidine tartrate ophthalmic solution (ALPHAGAN®) 0.2%, and effectively lowers IOP in patients with open-angle glaucoma or ocular hypertension by approximately 2-5 mmHg.

INDICATIONS AND USAGE

Brimonidine tartrate ophthalmic solution (ALPHAGAN®P) 0.15% is indicated for the lowering of intraocular pressure in patients with open-angle glaucoma or ocular hypertension.

CONTRAINDICATIONS

Brimonidine tartrate ophthalmic solution (ALPHAGAN®P) 0.15% 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 and contraindicated in neonates and infants (children under the age of 2 years).

PRECAUTIONS

General:
Children 2 years of age and above, especially those weighing ≤ 20 kg, should be treated with caution and closely monitored due to the high incidence and severity of somnolence. Please refer to Pediatric Use section.

Although brimonidine tartrate ophthalmic solution (ALPHAGAN®) 0.2% had minimal effect on the blood pressure and heart rate of patients in clinical studies, caution should be exercised in treating patients receiving brimonidine tartrate ophthalmic solution (ALPHAGAN®P) 0.15% with severe cardiovascular disease.

Brimonidine tartrate ophthalmic solution (ALPHAGAN®P) 0.15% has not been studied in patients with hepatic or renal impairment; caution should be used in treating such patients.

Brimonidine tartrate ophthalmic solution (ALPHAGAN®P) 0.15% 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. Delayed ocular hypersensitivity reactions have been reported with ALPHAGAN® 0.2%, with some reported to be associated with an increase in IOP.

Information for Patients:

As with other drugs in this class, brimonidine tartrate ophthalmic solution (ALPHAGAN®P) 0.15% 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. Brimonidine tartrate ophthalmic solution (ALPHAGAN®P) 0.15% may also cause blurred vision or visual disturbance in some patients. The patient should wait until these symptoms have cleared before driving or using machinery.

Drug Interactions:
Although specific drug interaction studies have not been conducted with brimonidine tartrate ophthalmic solution (ALPHAGAN®P) 0.15%, 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 (including ALPHAGAN® 0.2%), 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 brimonidine tartrate ophthalmic solution (ALPHAGAN®P) 0.15% in humans can lead to resulting interference with the IOP lowering effect. In experiments on rabbits, however, MAO inhibitors and tricyclic antidepressants did not alter the IOP response to brimonidine. No data on the level of circulating catecholamines after brimonidine tartrate ophthalmic solution (ALPHAGAN®P) 0.15% 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 brimonidine tartrate ophthalmic solution (ALPHAGAN®P) 0.15% 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 brimonidine tartrate ophthalmic solution (ALPHAGAN®P) 0.15%. 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. Brimonidine tartrate ophthalmic solution (ALPHAGAN®P) 0.15% 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 under the age of 2 years have not been established. Agitation, apnea, bradycardia, coma, convulsions, cyanosis, depression, dyspnea, emotional

instability, hypotension, hypothermia, hypotonia, hypoventilation, irritability, lethargy, pallor, respiratory depression, 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 in the eye, 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, ocular stinging sensation, foreign body sensation, headache, pharyngitis, photophobia, rash, rhinitis, sinus infection, sinusitis, stinging, superficial punctuate 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.

Post-marketing Experience
The following adverse reactions have been identified during postmarketing use of brimonidine tartrate ophthalmic solution (ALPHAGAN®P) 0.15% in clinical practice.

Eye disorders
Vision blurred, Conjunctivitis

General disorders and administration site conditions
Fatigue, Dizziness

Immune system disorders
Hypersensitivity

Nervous system disorders
Somnolence

OVERDOSAGE

Ophthalmic overdose: In those cases received, the events reported have generally been those already listed as adverse reactions.

Systemic overdose resulting from accidental ingestion: There is very limited information regarding accidental ingestion of brimonidine in adults. The only adverse event reported to date was hypotension. Treatment of an oral overdose includes supportive and symptomatic therapy; a patent airway should be maintained.

Symptoms of brimonidine overdose such as apnea, bradycardia, coma, hypotension, hypothermia, hypotonia, lethargy, pallor, respiratory depression, and somnolence have been reported in neonates, infants, and children receiving ALPHAGAN® as part of medical treatment of congenital glaucoma or by accidental oral ingestion (refer to Pediatric Use section).

DOSAGE AND ADMINISTRATION

The recommended dose is one drop of brimonidine tartrate ophthalmic solution (ALPHAGAN®P) 0.15% in the affected eye(s) three times daily, approximately 8 hours apart or as prescribed by the physician.

HOW SUPPLIED

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

5 mL in 10 mL bottle

NOTE: Store at temperatures not exceeding 25ºC. Keep out of reach of children.

CCDS v.2.1.

CAUTION: Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.

For suspected adverse drug reaction, report to FDA: www.fda.gov.ph. Seek medical attention at the first sign of ADR.

DR - XY28803

Revised Apr 2019
Date of First Authorization: Jul 2003

Allergan

Manufactured by:
Allergan Sales, LLC
Waco, Texas, U.S.A.

© 2020 Allergan. All rights reserved.
All trademarks are the property of their respective owners.

Imported & Distributed by:
Zuellig Pharma Corporation
Km. 14 West Service Road,
South Super Hi-way cor. Edison Ave.,
Brgy. Sun Valley, Parañaque City