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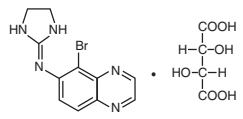
ALPHAGAN® P
(brimonidine tartrate ophthalmic solution) 0.1% sterile

DESCRIPTION

ALPHAGAN® P (brimonidine tartrate ophthalmic solution) 0.1% 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.

The structural formula is:



Formula: $C_{11}H_{10}BrN_5 \bullet C_4H_6O_6$ CAS Number: 70359-46-5

In solution, **ALPHAGAN® P** (brimonidine tartrate ophthalmic solution) 0.1% has a clear, greenish-yellow color. It has an osmolality of 250-320 mOsmol/kg and a pH of 7.4-8.0.

Each mL of **ALPHAGAN® P** contains:

Active ingredient: brimonidine tartrate 0.1% (1.0mg/mL)

Preservative: PURITE® 0.005% (0.05mg/mL)

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.

A 3-month (with a double-masked extension to 1 year) clinical study (N=433) was conducted to evaluate the safety, efficacy, and acceptability of **ALPHAGAN® P** 0.1% compared with **ALPHAGAN®** 0.2% administered 3 times daily in patients with glaucoma or ocular hypertension.

A 3-month analysis of the pivotal study indicated **ALPHAGAN® P** 0.1% is equivalent in IOP-lowering effect to **ALPHAGAN®** 0.2% and effectively lowers IOP in patients with glaucoma or ocular hypertension (mean change from baseline IOP -3.3 to -5.4mmHg).

Additionally, 12-month analysis of the pivotal study indicated **ALPHAGAN® P** 0.1% continued to be equivalent to **ALPHAGAN®** 0.2% and effectively lowered IOP in patients with glaucoma or ocular hypertension (mean change from baseline IOP at hours 0, 2, and 8 ranged from -2.7 to -5.4 mmHg). **ALPHAGAN® P** 0.1% is well-tolerated and provides a superior safety profile when compared with **ALPHAGAN®** 0.2%. **ALPHAGAN® P** 0.1% is the lowest effective dose of brimonidine tartrate that combines the IOP lowering efficacy with the most favorable safety and tolerability profile.

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 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 ≤20kg, should be treated with caution and closely monitored due to high incidence and severity of somnolence. Please refer to Pediatric Use section.

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 thromboangiitis obliterans.

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 activities such as driving and operating machinery should be cautioned of the potential for a decrease in mental alertness. **ALPHAGAN® P** 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 **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. In experiments on rabbits, however, tricyclic antidepressants did not alter the IOP response to brimonidine.

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 168 and 230 times the plasma drug concentration estimated in humans treated with one drop of **ALPHAGAN® P** ophthalmic solution 0.1% 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, and three *in vivo* studies in CD-1 mice: a host-mediated assay, cytogenetic assay, and dominant lethal assay.

Pregnancy: Teratogenic effects: Pregnancy Category B.

Reproduction and fertility studies in rats with brimonidine tartrate demonstrated no adverse effect on male or female fertility at doses which achieve up to approximately 477 times the systemic exposure following the maximum recommended human ophthalmic dose of **ALPHAGAN® P** 0.1%.

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 (1.65mg base/kg/day) and rabbits (3.33mg base/kg/day) achieved AUC exposure values 360- and 23-fold higher than similar values estimated in humans treated with **ALPHAGAN® P** 0.1%, 1 drop in both eyes three times daily. Since systemic accumulation is minimal, safety margins based on plasma drug concentration after both 2 and 3 times a day dosing are comparable.

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; 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:

In a 3-month, phase 3 study in children aged 2-7 years with glaucoma, inadequately controlled by beta- blockers, a high prevalence of somnolence (55%) was reported with **ALPHAGAN®** 0.2% as adjunctive treatment. In 8% of children, this was severe and led to discontinuation of treatment in 13%. The incidence of somnolence decreased with increasing age, being least in the 7-year-old age group (25%), but was more affected by weight, occurring more frequently in those children weighing ≤20 kg (63%) compared to those weighing >20 kg (25%).

Safety and effectiveness in pediatric patients under the age of 2 years have not been established. Apnea, bradycardia, coma, hypotension, hypothermia, hypotonia, lethargy, pallor, respiratory depression, and somnolence have been reported in neonates, infants, and children receiving brimonidine tartrate either for congenital glaucoma or by accidental ingestion.

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 and conjunctival hyperemia.

Adverse events occurring in approximately 5-9% of the subjects included: conjunctival folliculosis.

Events occurring in approximately 1-4% of subjects included: asthenia, burning sensation in the eye, conjunctivitis, erythema eyelid, eye pain, follicular conjunctivitis, foreign body sensation, ocular dryness/eye dryness, ocular pruritus/eye pruritus, oral dryness, somnolence, and superficial punctate keratitis.

Postmarketing Experience

The following adverse reactions have been identified during postmarketing use of **ALPHAGAN® P** 0.1% in clinical practice.

Eye disorders: Lacrimation increased, Vision blurred

Nervous system disorders: Dizziness, Headache

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 **ALPHAGAN® P** (brimonidine tartrate ophthalmic solution) 0.1% in the affected eye(s) three times daily, approximately 8 hours apart.

If more than one topical ophthalmic drug is to be used, the different drugs should be instilled at least 5 minutes apart.

HOW SUPPLIED:

ALPHAGAN® P 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 below 30°C. Keep out of reach of children.

Rx Only

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

Date of Revision: August 2023

Colors:

Black

Keyline

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abbvie	**File Upload Date:** 26 Sep 2023 14:49 UTC	**Version Number:** 3	**Artwork is created at 100%**
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