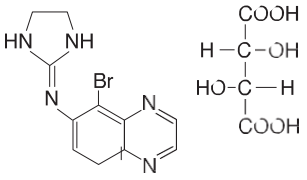
ALPHAGAN® P

(brimonidine tartrate) ophthalmic solution 0.1% w/v 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 the active ingredient brimonidine tartrate 0.1% (1 mg/mL) with the inactive ingredients sodium carboxymethylcellulose; sodium borate decahydrate; boric acid; sodium chloride; potassium chloride; calcium chloride dihydrate; magnesium chloride hexahydrate; PURITE® 0.005% (0.05 mg/mL) as a preservative; purified water; and hydrochloric acid and/or sodium hydroxide to adjust pH.

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 intraocular pressure (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).

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:

Although ALPHAGAN® had minimal effect on the blood pressure and heart rate of patients in clinical studies, caution should be exercised in treating patients receiving ALPHAGAN® with severe cardiovascular disease.

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, MAO inhibitors and 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 150 and 120 times, respectively, the plasma Cmax drug concentration in humans treated with one drop of ALPHAGAN® P ophthalmic solution 0.1% into both eyes 3 times per day, the recommended daily human dose. 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.

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 125 times the systemic exposure by C_{max} 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 (2.5mg/kg/day) and rabbits (5.0mg/kg/day) achieved AUC exposure values 360- and 20-fold higher, respectively, than similar values estimated in humans treated with ALPHAGAN® P 0.1%, 1 drop in both eyes three times daily.

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 of ALPHAGAN® P in children have not been established. During post-marketing surveillance, 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 (refer to Contraindications section).

Geriatric Use:

No overall differences in safety or effectiveness have been observed between elderly and other adult patients. The C_{max} and apparent half-life of brimonidine were similar in elderly subjects (65 years or older) and younger adults, indicating that its systemic absorption and elimination were not significantly affected by age.

ADVERSE REACTIONS

Clinical Trial Experience

Adverse event occurring in more than 20% of the subjects included: allergic conjunctivitis, in approximately 10-20% of the subjects included: conjunctival hyperemia and 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.

Post-marketing Experience

The following adverse reactions have been identified during post-marketing 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 of ALPHAGAN® P (brimonidine tartrate) ophthalmic solution 0.1% is 1 drop applied to the affected eye(s) three times a day at 8-hour intervals.

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 low density polyethylene (LDPE) plastic bottles with droppers with purple high impact polystyrene (HIPS) caps as follows:
5 mL in 10 mL bottle

NOTE: Store at or below 30°C. Keep out of reach of children.

Discard drug product 28 days after first opening.

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

CCDSv2.1

Date of Issue: DD MMM YYYY