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71816SN12

ALPHAGAN® P

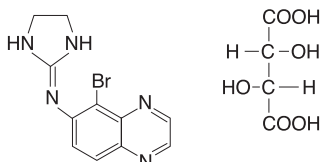
(brimonidine tartrate ophthalmic solution) 0.15%
sterile

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DESCRIPTION

ALPHAGAN® P (brimonidine tartrate ophthalmic solution) 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: $C_{11}H_{10}BrN_5 \cdot C_4H_6O_6$

CAS Number: 59803-98-4

In solution, ALPHAGAN® P (brimonidine tartrate ophthalmic solution) 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 ALPHAGAN® P contains:

Active ingredient: brimonidine tartrate 0.15% (1.5 mg/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.

Two clinical studies were conducted to evaluate the safety, efficacy, and acceptability of ALPHAGAN® P (brimonidine tartrate ophthalmic solution) 0.15% compared with ALPHAGAN® administered three-times-daily in patients with open-angle glaucoma or ocular hypertension. Those results indicated that ALPHAGAN® P (brimonidine tartrate ophthalmic solution) 0.15% is comparable in IOP lowering effect to ALPHAGAN® (brimonidine tartrate ophthalmic solution) 0.2%, and effectively lowers IOP in patients with open-angle glaucoma or ocular hypertension by approximately 2-5 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 brimonidine tartrate ophthalmic solution (ALPHAGAN® P 0.15%) had minimal effect on the blood pressure and heart rate of patients in clinical studies, caution should be exercised in treating patients receiving ALPHAGAN® P 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.

Patients prescribed IOP-lowering medication should be routinely monitored for IOP.

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 hazardous activities 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 86 and 55 times, respectively, the plasma drug concentration estimated in humans treated with one drop of ALPHAGAN® P 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.



* ARTWORK IS ACTUAL SIZE
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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 impaired fertility or harm to the fetus due to ALPHAGAN® P. 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. 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:

Safety and effectiveness in pediatric patients have not been established. During post-marketing surveillance, symptoms of 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 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%).

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

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 punctate 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.

Postmarketing Experience

The following adverse reactions have been identified during postmarketing use of ALPHAGAN® P 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 paediatric patients following inadvertent ingestion.

DOSAGE AND ADMINISTRATION

The recommended dose is one drop of ALPHAGAN® P (brimonidine tartrate ophthalmic solution) 0.15% 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:

3 mL in 10 mL bottle

5 mL in 10 mL bottle

10 mL in 10 mL bottle

15 mL in 15 mL bottle

NOTE: Store below 25°C. Keep out of reach of children.

Rx Only

Manufactured by:

Allergan Sales, LLC

Waco, Texas, U.S.A.

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Date of Revision: April 2014



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