ALPHAGAN® 0.2%
Brimonidine tartrate ophthalmic solution 0.2%

DESCRIPTION

Each mL contains: brimonidine tartrate 2 mg (equivalent to 1.32 mg as brimonidine free base) with: benzalkonium chloride 0.05 mg, polyvinyl alcohol 14 mg; sodium chloride; sodium citrate; citric acid and purified water.

CLINICAL PHARMACOLOGY

ALPHAGAN® 0.2% is a relatively selective alpha-2 adrenergic 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.

After ocular administration of a 0.2% 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.

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. ALPHAGAN® 0.2% has the action of lowering intraocular pressure with minimal effect on cardiovascular and pulmonary parameters.

In comparative clinical studies with timolol 0.5%, lasting up to one year, the IOP lowering effect of ALPHAGAN® 0.2% was approximately 4-6 mm Hg compared with approximately 6 mm Hg for timolol. Eight percent of subjects were discontinued from studies due to inadequately controlled intraocular pressure, which in 30% of these patients occurred during the first month of therapy. Approximately 20% were discontinued due to adverse experiences.

INDICATIONS AND USAGE

ALPHAGAN® 0.2% is indicated for lowering intraocular pressure in patients with open-angle glaucoma or ocular hypertension. The IOP lowering efficacy of ALPHAGAN® 0.2% ophthalmic solution diminishes over time in some patients. This loss of effect appears with a variable time of onset in each patient and should be closely monitored.

CONTRAINDICATIONS

ALPHAGAN® 0.2% 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® 0.2% had minimal effect on blood pressure and heart rate of patients in clinical studies, caution should be exercised in treating patients receiving ALPHAGAN® 0.2% with severe cardiovascular disease.

ALPHAGAN® 0.2% has not been studied in patients with hepatic or renal impairment; caution should be used in treating such patients.

ALPHAGAN® 0.2% should be used with caution in patients with depression, cerebral or coronary insufficiency,

Raynaud's phenomenon, orthostatic hypotension or thromboangiitis obliterans.

During the studies there was a loss of effect in some patients. The IOP-lowering efficacy observed with ALPHAGAN® 0.2% ophthalmic solution during the first month of therapy may not always reflect the long-term level of IOP reduction. For those patients whose IOP is not adequately controlled with twice-daily dosing, an additional drop of brimonidine in the afternoon can be added. Patients prescribed IOP-lowering medication should be routinely monitored for IOP.

Information for Patients: The preservative in ALPHAGAN® 0.2%, 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® 0.2% to insert soft contact lenses.

As with other drugs in this class, ALPHAGAN® 0.2% 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.

Drug Interactions: Although specific drug interaction studies have not been conducted with ALPHAGAN® 0.2%, the possibility of an additive or potentiating effect with CNS depressants (alcohol, barbiturates, opiates, sedatives or anesthetics) should be considered. ALPHAGAN® 0.2% did not have significant effects on pulse and

blood pressure in clinical studies. However, since 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 ALPHAGAN® 0.2% can lead to an interference in IOP lowering effect. No data on the level of circulating catecholamines after ALPHAGAN® 0.2% is instilled 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 21 month and 2 year studies in mice and rats given oral doses of 2.5 mg/kg/day (as the free base) and 1.0 mg/kg/day, respectively (~77 and 118 times, respectively, the human plasma drug concentration following the recommended ophthalmic dose).

ALPHAGAN® 0.2% was not mutagenic or cytogenic in a series of *in vitro* and *in vivo* studies including the Ames test, host-mediated assay, chromosomal aberration assay in Chinese Hamster Ovary (CHO) cells, cytogenic studies in mice and dominant lethal assay.

Pregnancy: Reproduction 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® 0.2%. Dosing at this level produced 100 times the
plasma drug concentration level seen in humans following multiple ophthalmic doses.

There are no studies of ALPHAGAN® 0.2% in pregnant women, however in animal studies, brimonidine crossed the placenta and entered into the fetal circulation to a limited extent. ALPHAGAN® 0.2% 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 ALPHAGAN® 0.2% is excreted in human milk, although in animal studies, brimonidine tartrate has been shown to be 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. Symptoms of bradycardia, hypotension, hypothermia, hypotonia and apnea have been reported (rarely) in neonates receiving brimonidine.

ADVERSE REACTIONS

Adverse events occurring in approximately 10-30% of the subjects, in

descending order of incidence, included oral dryness, ocular hyperemia, burning and stinging, headache, blurring, foreign body sensation, fatigue/drowsiness, conjunctival follicles, ocular allergic reactions and ocular pruritus.

Events occurring in approximately 3-9% of the subjects, in descending order included corneal staining/erosion, photophobia, eyelid erythema, ocular ache/pain, ocular dryness, tearing, upper respiratory symptoms, eyelid edema, conjunctival edema, dizziness, blepharitis, ocular irritation, gastrointestinal symptoms, asthenia, conjunctival blanching, abnormal vision and muscular pain.

The following adverse reactions were reported in less than 3% of the patients: lid crusting, conjunctival hemorrhage, abnormal taste, insomnia, conjunctival discharge, depression, hypertension, anxiety, palpitations, nasal dryness and syncope.

Postmarketing Events

The following adverse reactions have been identified during postmarketing use of ALPHAGAN® 0.2% in clinical practice. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made.

Eye disorders
Iritis, iridocyclitis (anterior uveitis), Miosis, Conjunctivitis, Eyelids pruritus

Immune system disorders
Hypersensitivity, Skin reaction (including Erythema, Face edema, Pruritus, Rash, and Vasodilatation)

Cardiac disorders
Palpitations/arrhythmias (including bradycardia or tachycardia)

Psychiatric disorders
Depression

Vascular disorders
Hypotension, Syncope

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

The recommended dose is one drop of ALPHAGAN® 0.2% in the affected eye(s) two times daily. For those patients whose IOP peaks in the afternoon or need additional IOP control, an additional drop of brimonidine in the afternoon can be added.

HOW SUPPLIED

ALPHAGAN® 0.2% ophthalmic solution is supplied sterile in white opaque plastic dropper bottles as follows: 5 mL, 10 mL, 15 mL.

NOTE: Store at or below 25C (77F). On prescription only. Keep out of the reach of children.

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Manufactured by:
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