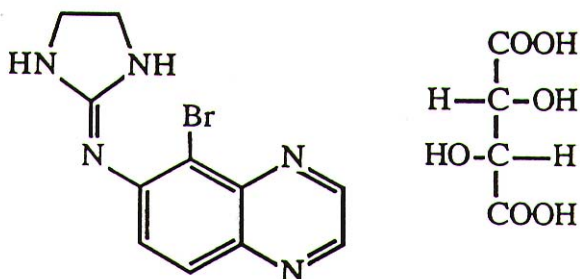


ALPHAGAN[®] Eye Drops

NAME OF THE DRUG

The active constituent of ALPHAGAN[®] eye drops is brimonidine tartrate.



(structure of brimonidine tartrate)

CAS Registry No.: 79570-19-7

DESCRIPTION

Brimonidine tartrate (ALPHAGAN[®] ophthalmic solution 0.2%) is an alpha-2 selective adrenergic agonist for ophthalmic use. Brimonidine tartrate is an off-white, pale yellow to pale pink powder and is water soluble (34 mg/mL). In solution, brimonidine tartrate has a clear, greenish-yellow colour.

Chemical name: 5-bromo-6-(2-imidazolidinylideneamino) quinoxaline L-tartrate.

Molecular weight: 442.24 as the tartrate salt.

Empirical formula: C₁₁H₁₀BrN₅, C₄H₆O₆

ALPHAGAN[®] 0.2% is a sterile ophthalmic solution. Each mL of ALPHAGAN[®] solution contains:

ACTIVE: brimonidine tartrate 2.0 mg (equivalent to 1.32 mg as brimonidine free base)

PRESERVATIVE: benzalkonium chloride 0.05 mg

INACTIVES: polyvinyl alcohol; sodium chloride; sodium citrate; citric acid; and purified water. Hydrochloric acid and/or sodium hydroxide may be added to adjust pH (6.3-6.5).

PHARMACOLOGY

Mechanism of action

Brimonidine tartrate is an alpha-2 adrenergic agonist that is 1000-fold more selective for the alpha-2 adrenoceptor than the alpha-1 adrenergic receptor. Affinity at human alpha-1 and alpha-2 adrenoceptors are ~2000 nM and ~2 nM, respectively. This selectivity results in no mydriasis and the absence of vasoconstriction in microvessels associated with human retinal xenografts.

Topical administration of brimonidine solution decreases intraocular pressure (IOP) in humans. When used as directed, brimonidine eye drops have the action of reducing elevated IOP with minimal effect on cardiovascular parameters.

Brimonidine has a rapid onset of action, with the peak ocular hypotensive effect occurring at two hours post-dosing. The duration of effect is 12 hours or greater.

Fluorophotometric studies in animals and humans, suggest that brimonidine solution has a dual mechanism of action. Brimonidine lowers IOP by reducing aqueous humor production and enhancing uveoscleral outflow.

Pharmacokinetics

After ocular administration of a 0.2% solution twice daily in normal healthy subjects for 10 days, plasma concentrations were measured as (mean) C_{max} 0.06 ng/mL. Plasma concentrations peaked within 1 to 4 hours and declined with a systemic half-life of approximately 3 hours.

Brimonidine is metabolized primarily by the liver. Urinary excretion is the major route of elimination of the drug and its metabolites. Approximately 87% of the radioactivity following an orally-administered radioactive dose was eliminated within 120 hours, with 74% found in the urine.

Clinical Studies

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

MONOTHERAPY

The efficacy of ALPHAGAN® eye drops was demonstrated in two multicentre studies comparative with timolol 0.5% lasting up to one year in subjects with glaucoma or ocular hypertension. A total of 513 subjects received ALPHAGAN® eye drops in the two studies.

The overall mean decrease (\pm SD) in IOP from baseline at 12 months, as measured at peak response, was 6.20 ± 4.08 mmHg for brimonidine monotherapy and 5.56 ± 3.65 mmHg for timolol monotherapy. At trough response, these figures were 3.74 ± 3.83 mmHg for brimonidine and 5.80 ± 3.35 mmHg for timolol.

These results represent approximately 16% - 26% mean reduction from baseline measurements. IOP decreases were maintained for up to one year; no tachyphylaxis was observed. 9.4% of subjects treated with ALPHAGAN® eye drops and 5.1% of subjects treated with timolol 0.5% were discontinued because of inadequately controlled intraocular pressure. 30% of these patients withdrew during the first month of therapy.

ADJUNCTIVE THERAPY

The ability of ALPHAGAN® eye drops to lower IOP when used in combination with other anti-glaucoma agents has been evaluated in two large scale multicentre, randomised studies, involving 321 patients, 150 of which received brimonidine.

In the first study, brimonidine 0.2% twice daily as an adjunct to β -blocker therapy was compared with pilocarpine 2% administered three times daily, as an adjunct to β -blocker therapy. The overall mean decrease (\pm SD) in IOP from baseline at 3 months, as measured at peak response, was 4.92 ± 3.02 mmHg for brimonidine adjunctive therapy and 5.52 ± 3.08 mmHg for pilocarpine adjunctive therapy. At trough response, these figures were 3.95 ± 2.67 mmHg for brimonidine adjunctive therapy and 3.81 ± 2.75 mmHg for pilocarpine adjunctive therapy. These results represent a mean additional decrease in IOP for ALPHAGAN® adjunctive therapy of 17% - 22%.

The second study was an 8 month comparison of the additive IOP lowering effect to an already established β -blocker eye drop regimen, of ALPHAGAN® 0.2% eye drops or dipivefrine 0.1% eye

drops. Adjunctive ALPHAGAN® eye drops was shown to be superior to adjunctive dipivefrine 0.1% at peak effect and equivalent in efficacy to adjunctive dipivefrine at trough at most time points.

The overall mean decrease (\pm SD) in IOP from baseline at 3 months, as measured at peak response, was 3.26 ± 3.16 mmHg for ALPHAGAN® adjunctive therapy and 2.33 ± 3.13 mmHg for dipivefrine adjunctive therapy. At trough response, these figures were 2.89 ± 3.14 mmHg for ALPHAGAN® adjunctive therapy and 3.31 ± 3.69 mmHg for dipivefrine adjunctive therapy. These results represent a mean additional decrease in IOP for brimonidine adjunctive therapy of 12% - 15%.

INDICATIONS AND USE

ALPHAGAN® eye drops are effective in lowering elevated intraocular pressure in patients with chronic open angle glaucoma or ocular hypertension. ALPHAGAN® eye drops can be used in the treatment of glaucoma as either monotherapy or in combination with topical beta-blockers.

CONTRAINDICATIONS

ALPHAGAN® eye drops are contraindicated in patients with hypersensitivity to brimonidine tartrate or any component of this medication. This product is also contraindicated in patients receiving monoamine oxidase (MAO) inhibitor therapy.

PRECAUTIONS

General

Although brimonidine eye drops had minimal effect on blood pressure and heart rate of patients in clinical studies, caution should be observed in treating patients with severe, uncontrolled cardiovascular disease.

Brimonidine eye drops have not been studied in patients with hepatic or renal impairment; caution should be used in treating such patients.

Brimonidine eye drops should be used with caution in patients with depression, cerebral or coronary insufficiency, Raynaud's phenomenon, orthostatic hypotension or thromboangitis obliterans.

During the studies there was a loss of effect in some patients. The IOP-lowering efficacy observed with brimonidine eye drops during the first month of therapy may not always reflect the long-term level of IOP reduction. Patients prescribed IOP-lowering medication should be routinely monitored for IOP.

Information for Patients: The preservative in brimonidine eye drops, benzalkonium chloride, may be absorbed by soft contact lenses. Patients wearing soft contact lenses should be instructed to wait at least 15 minutes after using brimonidine eye drops to insert soft contact lenses.

As with other alpha-agonists, brimonidine can potentially cause fatigue and/or drowsiness in some patients. Patients who engage in hazardous activities requiring mental alertness, including driving, should be cautioned of the potential for a decrease in mental alertness.

Drug Interactions:

Specific drug interaction studies have not been conducted with brimonidine eye drops. The possibility of an additive or potentiating effect with CNS depressants (alcohol, barbiturates, opiates, sedatives, or anesthetics) should be considered. Because brimonidine eye drops may reduce blood pressure, caution using drugs such as antihypertensives and/or cardiac glycosides is advised.

Caution is advised when initiating or changing the dose of a concomitant systemic agent which may interact with alpha-adrenergic agonists or interfere with their activity (i.e. sympathomimetic agents, agonists or antagonists of the adrenergic receptor).

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 can lead to an interference in IOP lowering effect. No data on the level of circulating catecholamines after brimonidine eye drops are instilled are available. Caution, however, is advised in patients taking tricyclic antidepressants which can affect the metabolism and uptake of circulating amines.

As brimonidine is metabolised primarily by the liver, most likely by cytochrome P450 and aldehyde oxidase, this may affect the metabolism of other drugs that utilise the cytochrome P450 pathway.

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 and 1 mg/kg/day respectively as the free base. Plasma concentrations of brimonidine in mice and rats in the high-dose groups were ≥ 60 times greater than those expected in humans dosed therapeutically.

Brimonidine was non-genotoxic in assays for chromosomal damage (Chinese hamster cells in vitro, in vivo bone marrow cytogenetic assay and a dominant lethal assay). In assays for gene mutations in *S. typhimurium* and *E. coli*, brimonidine gave a positive response in one *S. typhimurium* strain without metabolic activation. Other strains gave negative results.

Brimonidine did not have a significant effect on fertility in a reproductive performance study in rats at oral doses of up to 0.66 mg/kg/day.

Pregnancy: Pregnancy Category B1.

There are no studies of brimonidine in pregnant women, but in rats the drug crosses the placenta and enters the fetal circulation.

In pregnant rats, brimonidine was associated with maternotoxicity and increased early absorptions/post-implantation losses and decreased pup viability and bodyweights at exposures (based on AUC) of 180 times greater than expected exposures in humans treated therapeutically. The drug was also maternotoxic in rabbits and caused abortions at exposures about 12 times greater than those expected in humans. In both rats and rabbits, brimonidine was not teratogenic.

Use in Lactation: It is not known whether brimonidine is excreted in human milk. In lactating rats, levels of the drug in milk were up to 12 times higher than those in maternal plasma; and in a peri- and postnatal study in rats, brimonidine was associated with decreased pup viability and pup weights during lactation at maternal plasma exposures of about 55 times greater than those expected in humans.

Paediatric Use: Safety and effectiveness in paediatric patients have not been established. Symptoms of bradycardia, hypotension, hypothermia, hypotonia and apnea have been reported (rarely) in neonates receiving brimonidine.

ADVERSE REACTIONS

A: Clinical Trials - Frequency of adverse events occurring in pivotal monotherapy studies

	<i>brimonidine 0.2%</i> (n=822) %	<i>timolol 0.5%</i> (n=521) %	<i>betaxolol 0.25%</i> (n=196) %
OCULAR			
<i>oral dryness</i>	21	13	1.0
<i>ocular hyperemia</i>	20	21	7.7
<i>burning/stinging</i>	19	35.5	7.1
<i>foreign body sensation</i>	12	13	0
<i>blurring</i>	12	18	2.6
<i>ocular allergic reaction</i>	8.9	0.2	0
<i>conjunctival follicles</i>	8.5	4.4	1.0
<i>ocular pruritus (itching)</i>	7.8	8.8	1.0
<i>corneal staining/erosion</i>	6.8	9.2	4.1
<i>conjunctival oedema</i>	6.3	5.0	3.1
<i>photophobia</i>	6.0	8.4	0.5
<i>eyelid erythema</i>	5.2	4.4	0
<i>ocular dryness</i>	5.2	8.3	0.5
<i>ocular ache/pain</i>	5.1	4.2	2.6
SYSTEMIC			
<i>headache</i>	13	17	5.6
<i>fatigue/drowsiness</i>	12	13	1.0
<i>upper respiratory symptoms</i>	6.7	7.1	4.1

Brimonidine eye drops - adverse events occurring at 1-5%

Ocular: eyelid oedema, abnormal vision, blepharitis, ocular irritation, conjunctival blanching, conjunctival discharge.

Systemic: dizziness, gastrointestinal symptoms, asthenia, abnormal taste.

Brimonidine eye drops - adverse events occurring at <1%

Ocular: conjunctival papillae, tearing.

Systemic: depression, systemic allergic reaction, nasal dryness, palpitations.

B: Clinical Trials - Frequency of adverse events occurring in combination therapy studies

As adjunctive therapy, assigning causality of adverse events cannot be reliable because both agents are administered concurrently. However, the most common adverse events have been tabulated below.

	<i>brimonidine 0.2%</i> <i>in combination</i> <i>with various beta</i> <i>blockers (n=185)</i> %	<i>pilocarpine 2.0%</i> <i>in combination with</i> <i>various beta</i> <i>blockers (n=66)</i> %	<i>dipivefrine 0.1%</i> <i>in combination with</i> <i>various beta</i> <i>blockers (n=69)</i> %
OCULAR			
<i>Burning/stinging</i>	8.6	4.5	18.8
<i>Conjunctival blanching</i>	4.3	0	34.8
<i>Ocular allergic reaction</i>	10.3	0	11.6
<i>Ocular ache/pain</i>	3.8	6.1	1.4

<i>Ocular hyperemia</i>	9.7	0	37.7
<i>Conjunctival follicles</i>	1.6	0	5.8
SYSTEMIC			
<i>Oral dryness</i>	9.7	0	5.8
<i>Headache</i>	6.5	24.2	5.8

Post Marketing Experience

Symptoms of bradycardia, hypotension, hypothermia, hypotonia and apnea have been reported (rarely) in neonates receiving brimonidine.

DOSAGE AND ADMINISTRATION

Monotherapy: The recommended dose is one drop of ALPHAGAN® eye drops in the affected eye(s) twice daily, approximately 12 hours apart.

Combination Therapy: The recommended dose is one drop of ALPHAGAN® eye drops in the affected eye(s) twice daily, approximately 12 hours apart.

In order to minimise systemic absorption of ALPHAGAN® eye drops, apply pressure to the tear duct immediately following administration of the drug.

As with all eye drops containing benzalkonium chloride as a preservative, there is potential for incompatibility with other topical ophthalmic medications. If more than one topical ophthalmic drug is to be used, other eye drops should not be used within five to ten minutes of using ALPHAGAN® eye drops.

To avoid contamination of the solution, keep container tightly closed. Do not touch dropper tip to any surface. Discard contents 4 weeks after opening the bottle. Contents are sterile if seal is intact.

OVERDOSAGE

Ophthalmic overdose:

There is no experience in adults with the unlikely case of an overdose via the ophthalmic route. However, symptoms of brimonidine overdose such as hypotension, bradycardia, hypothermia and apnea have been reported in a few neonates receiving ALPHAGAN® as part of medical treatment of congenital glaucoma.

Systemic overdose resulting from accidental ingestion:

No instances of human adult ingestion of ALPHAGAN® are known. Oral overdoses of other alpha-2 agonists have been reported to cause symptoms such as hypotension, asthenia, vomiting, lethargy, sedation, bradycardia, arrhythmias, miosis, apnea, hypotonia, hypothermia, respiratory depression and seizure.

PRESENTATION:

ALPHAGAN® (brimonidine tartrate ophthalmic solution) 0.2% sterile solution is supplied in white opaque plastic dropper bottles.

Eye drops: 5 mL
Storage: Store below 25°C.
Shelf life: 24 months

AUST R 60297

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