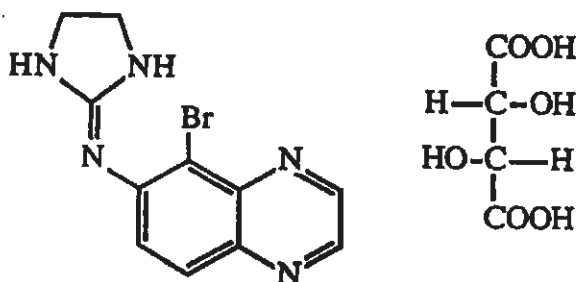


ALPHAGAN[®] P 1.5 Eye Drops

NAME OF THE DRUG

The active constituent of ALPHAGAN[®] P 1.5 eye drops is brimonidine tartrate.



(structure of brimonidine tartrate)

CAS Registry No.: 79570-19-7

DESCRIPTION

Brimonidine tartrate is an off-white, pale yellow to pale pink powder and is soluble in water (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[®] P 1.5 0.15% is a sterile ophthalmic solution. Each mL of ALPHAGAN[®] P 1.5 solution contains:

ACTIVE: brimonidine tartrate 1.5 mg (equivalent to 0.99 mg as brimonidine free base)

PRESERVATIVE: Sodium chlorite (as PURITE)[®] 1.8µg

INACTIVES: Carmellose sodium, boric acid, borax, sodium chloride, potassium chloride, calcium chloride, magnesium chloride and purified water. Hydrochloric acid and/or sodium hydroxide may be added to adjust pH (6.6-7.4)

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. Affinities 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 tartrate has a dual mechanism of action. ALPHAGAN[®] P 1.5 eye drops lower IOP by reducing aqueous humor production and enhancing uveoscleral outflow.

Pharmacokinetics

After ocular administration of a 0.1% and 0.2% solution of ALPHAGAN[®] P 1.5 eye drops three times daily for 7 days, plasma concentrations were low (mean C_{max} was 0.03 ng/mL and 0.06 ng/mL for the 0.1% and 0.2% solutions, respectively). There was a slight accumulation in plasma after multiple instillations. The area under the plasma concentration-time curve over 8 hours at steady state (AUC_{0-8h}) was 0.14 ng.hr/mL and 0.25 ng.hr/mL for the 0.1% and 0.2% solutions, respectively. The mean apparent half-life in the systemic circulation was approximately 2 hours in humans after topical dosing.

Peak plasma brimonidine concentration (C_{max}) is predicted to be 0.03 ng/mL when ALPHAGAN[®] P 1.5 is administered twice daily for 7 days.

In humans, brimonidine is primarily metabolised extensively in 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. The pharmacokinetics of ALPHAGAN[®] P 1.5 eye drops have not been specifically studied in patients with hepatic or renal disease (see Warnings and Precautions) or in paediatric patients (see Contraindications and Dosage and Administration).

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.

Studies with ALPHAGAN[®] eye drops

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%.

Studies with ALPHAGAN[®] P 1.5 eye drops

The efficacy and safety of ALPHAGAN[®] P 1.5 eye drops was demonstrated by comparison with that of ALPHAGAN[®] eye drops in a 3 month multicentre study involving 407 patients with glaucoma or ocular hypertension already controlled with ALPHAGAN[®] eye drops (study 017). ALPHAGAN[®] P eye drops used twice daily were found to provide non-inferior efficacy compared to ALPHAGAN[®] eye drops used twice daily, with the upper limit of the 95% confidence interval around the difference in mean IOP change from baseline between ALPHAGAN[®] P 1.5 and ALPHAGAN[®] being no more than 0.79 mm at any timepoint (NS). ALPHAGAN[®] P 1.5 eye drops also tended towards less overall adverse reactions than ALPHAGAN[®] eye drops (16.7% vs 22.1%) and less allergic conjunctivitis (3.9% vs 4.4%). The most frequently reported adverse reaction was conjunctival hyperaemia (7.9% vs 3.9%).

The long-term safety of ALPHAGAN[®] P 1.5 eye drops was confirmed by comparison with that of ALPHAGAN[®] eye drops in two multicentre studies of 12 months duration. In these studies, patients were randomised to brimonidine 0.15% (ALPHAGAN[®] P 1.5) eye drops three times daily, brimonidine-Purite[®] 0.2% eye drops three times daily, or brimonidine 0.2% (ALPHAGAN[®]) eye drops three times daily. Pooled data from these studies demonstrated that ALPHAGAN[®] P 1.5 eye drops were associated with significantly less adverse reactions than ALPHAGAN[®] eye drops overall (49.7% vs 62.4%), as well as in terms of the following specific adverse reactions: allergic conjunctivitis (9.2% vs 15.7%), eye discharge (1.3% vs 3.9%), conjunctival hyperaemia (18.2% vs 25.6%) and oral dryness (5.3% vs 10.4%). Similarly, ALPHAGAN[®] P 1.5 eye drops were associated with significantly less adverse reactions than brimonidine-Purite[®] 0.2% for allergic conjunctivitis (9.2% vs 14.6%) and oral dryness (5.3% vs 9.4%). Brimonidine-Purite[®] 0.2% eye drops were also associated with less adverse reactions than ALPHAGAN[®] eye drops for allergic conjunctivitis (14.6% vs 15.7%) and oral dryness (9.4% vs 10.4%) suggesting a safety benefit from PURITE[®] substitution, even when brimonidine concentration was unchanged. These safety data

support those of study 017, and demonstrate that ALPHAGAN[®] P 1.5 eye drops provide the most favourable safety profile with the lowest effective dose of brimonidine.

INDICATIONS AND USE

ALPHAGAN[®] P 1.5 eye drops are effective in lowering elevated intraocular pressure in patients with chronic open angle glaucoma or ocular hypertension. ALPHAGAN[®] P 1.5 eye drops can be used in the treatment of glaucoma as either monotherapy or in combination with topical beta-blockers.

CONTRAINDICATIONS

ALPHAGAN[®] P 1.5 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.

ALPHAGAN[®] P 1.5 eye drops are contraindicated in infants and children <2 years of age.

PRECAUTIONS

General

Although ALPHAGAN[®] P 1.5 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.

ALPHAGAN[®] P 1.5 eye drops have not been studied in patients with hepatic or renal impairment; caution should be used in treating such patients.

ALPHAGAN[®] P 1.5 eye drops 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 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: 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:

Although specific drug interaction studies have not been conducted with ALPHAGAN[®] P 1.5 eye drops, the possibility of an additive or potentiating effect with CNS depressants (alcohol, barbiturates, opiates, sedatives, or anesthetics) should be considered.

Because ALPHAGAN[®] P 1.5 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 (ie. 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 ALPHAGAN[®] P 1.5 eye drops can lead to an interference in IOP lowering effect, although in rabbit experiments, tricyclic antidepressants did not alter the IOP response to brimonidine. No data on the level of circulating catecholamines after ALPHAGAN[®] P 1.5 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.

Genotoxicity

Brimonidine tartrate 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 *Salmonella typhimurium* and *Escherichia coli*, brimonidine gave a positive response in one *S.typhimurium* strain without metabolic activation. Other strains gave negative results.

Carcinogenicity

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 and 1.0 mg/kg/day brimonidine respectively. Plasma concentrations of brimonidine in mice and rats in the high dose groups were at least 110 times greater than those expected in humans dosed therapeutically.

Effects on Fertility

Brimonidine did not have a significant effect on fertility in rats at oral doses of up to 0.66 mg/kg/day (*ca* 115 times the anticipated AUC in patients).

Use in Pregnancy: Category B3

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

In pregnant rats, brimonidine was associated with maternotoxicity and increased early resorptions/post-implantation losses and decreased pup viability and body weights at estimated exposures (based on AUC) of 390 times the expected exposures in humans treated therapeutically. The drug was also maternotoxic in rabbits and caused abortions at exposures about 26 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 perinatal and postnatal study in rats, brimonidine was associated with decreased pup viability and pup weights during lactation at maternal plasma exposures of about 116 times greater than those expected in humans.

Paediatric Use:

Safety and effectiveness of ALPHAGAN® P 1.5 eye drops in children has 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 either for congenital glaucoma or by accidental ingestion. Also see Contraindications section.

ADVERSE REACTIONS

The most commonly reported adverse reaction is conjunctival hyperaemia, occurring in 18.2% of patients. This is usually transient and does not normally require discontinuation of treatment. Allergic conjunctivitis occurred in 9.2% of subjects (causing withdrawal in 7.4% of subjects) in clinical trials, with the onset between 3 and 9 months in the majority of patients.

The following undesirable effects considered to be at least possibly related to treatment were reported during two 12-month clinical trial studies where ALPHAGAN® P 1.5 eye drops were administered three times daily:

Ocular effects:

Very common	Conjunctival hyperaemia
Common	Allergic conjunctivitis, ocular irritation (ocular burning and stinging sensation, eye pruritus, foreign body sensation, follicular conjunctivitis, conjunctival folliculosis, conjunctival oedema), local irritation (eyelid oedema and erythema, eye discharge, blepharitis, eye pain), eye dryness, epiphora, photophobia, superficial punctate keratitis, visual disturbance, worsening of visual acuity
Uncommon	Eye oedema, eyelid pruritus, conjunctivitis, papillary hypertrophy, iritis

Systemic effects:

Common	<i>Body as a whole:</i> Asthenia, headache <i>Gastrointestinal:</i> Oral dryness <i>Respiratory system:</i> Rhinitis
Uncommon	<i>Nervous system:</i> Somnolence, dizziness <i>Respiratory system:</i> Pharyngitis <i>Special senses:</i> Taste perversion

In another 3-month clinical study in patients whose IOP was already controlled with ALPHAGAN® eye drops, ALPHAGAN® P 1.5 eye drops dosed twice daily was evaluated. The undesirable effects considered to be at least possibly related to treatment were similar to those seen in the 12-month three times daily studies, but the incidence rates were generally lower.

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

Immune system disorders

Not known: Hypersensitivity

Eye disorders

Not known: Vision blurred

General disorders and administration site conditions

Not known: Fatigue

DOSAGE AND ADMINISTRATION

The recommended dose is one drop of ALPHAGAN® P 1.5 eye drops in the affected eye(s) twice daily, approximately 12 hours apart.

If more than one topical ophthalmic medicine is to be used, other eye drops should not be used within five to ten minutes of using ALPHAGAN® P 1.5 eye drops.

In order to minimise systemic absorption of ALPHAGAN® P 1.5 eye drops, apply pressure to the tear duct immediately following administration.

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

Adults

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.

Paediatric population

Symptoms of brimonidine overdose such as apnoea, 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.

Oral overdoses of other α_2 -agonists have been reported to cause symptoms such as hypotension, asthenia, vomiting, lethargy, sedation, bradycardia, arrhythmias, miosis, apnoea, hypotonia, hypothermia, respiratory depression and seizure.

Treatment of an oral overdose includes supportive and symptomatic therapy; a patent airway should be maintained.

In the event of a topical overdosage, flush eye with a topical ocular irrigant.

PRESENTATION:

ALPHAGAN[®] P 1.5 (brimonidine tartrate ophthalmic solution) 0.15% sterile solution is supplied in plastic dropper bottles.

Eye drops: 5 mL

Storage: Store below 25°C.

Shelf life: 18 months

AUST R 158888

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Poisons schedule: S4

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