AUSTRALIAN PRODUCT INFORMATION

ALPHAGAN® P 1.5 (BRIMONIDINE TARTRATE) EYE DROPS

1 NAME OF THE MEDICINE

Brimonidine tartrate

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL of ALPHAGAN® P eye drops contains brimonidine tartrate 1.5 mg (equivalent to 0.99 mg as brimonidine free base).

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Eye drops, solution.

ALPHAGAN® P 1.5 0.15% is a sterile ophthalmic solution.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

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.

4.2 DOSE AND METHOD OF 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.

4.3 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.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Identified precautions

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.

Cardiovascular disease

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 receiving ALPHAGAN® P 1.5 with severe, uncontrolled cardiovascular disease.

Hypersensitivity

Delayed ocular hypersensitivity reactions have been reported with ALPHAGAN®, with some reported be associated with an increase in IOP.

Use in hepatic and renal impairment

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.

Use in the elderly

No data available.

Paediatric use

Safety and effectiveness of ALPHAGAN® P 1.5 eye drops in children has not been established; however, during post-marketing surveillance, apnoea, 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 oral ingestion. [See Section 4.3 CONTRAINDICATIONS.]

Children 2 years of age and above, especially those weighing ≤ 20 kg, should be treated with caution and closely monitored due to the high incidence and severity of somnolence.

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, such as

driving and operating machinery, should be cautioned of the potential for a decrease in mental alertness.

Patients should be instructed to avoid allowing the tip of the dispensing container to contact the eye or surrounding structures to avoid eye injury and contamination of eye drops.

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF 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 beta-blockers (ophthalmic and systemic),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.

4.6 FERTILITY, PREGNANCY AND LACTATION

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 – Pregnancy Category B3

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

Because animal reproductive studies are not always predictive of human response, ALPHAGAN® P 1.5 should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the foetus.

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. Therefore, a decision should be made whether to discontinue the drug, taking into account the importance of the drug to the mother. 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.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

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, such as driving and operating machinery, should be cautioned of the potential for a decrease in mental alertness.

ALPHAGAN® P 1.5 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.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

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	*Body as a whole:*	Asthenia, headache
	Gastrointestinal:	Oral dryness
	Respiratory system:	Rhinitis
Uncommon	*Nervous system:*	Somnolence, dizziness
	Respiratory system:	Pharyngitis
	Special senses:	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.

Post marketing experience

The following adverse reactions have been identified during post-marketing use of ALPHAGAN® P 1.5 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, conjunctivitis

General disorders and administration site conditions:

Not known: Fatigue, dizziness

Nervous system disorders

Somnolence

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

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.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Brimonidine tartrate is an alpha-2 adrenergic agonist that is 1000-fold more selective for the alpha-2 adrenoreceptor than the alpha-1 adrenergic receptor. Affinities at human alpha-1 and alpha-2 adrenoreceptors 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.

Clinical trials

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 (± 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 (± 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 (± 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 ± 3.14mmHg 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.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

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 ($AUC_{0\text{-}8h}$) 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.

Metabolism

In humans, brimonidine is primarily metabolised extensively in the liver.

Excretion

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 Precautions) or in paediatric patients (see Contraindications and Dosage and Administration).

5.3 PRECLINICAL SAFETY DATA

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.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

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 dihydrate, magnesium chloride hexahydrate, and purified water. Hydrochloric acid and/or sodium hydroxide may be added to adjust pH (6.6-7.4).

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

18 months.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C.

To avoid contamination of the solution, keep container tightly closed. Do not touch dropper tip to any surface. Contents are sterile if seal is intact.

6.5 NATURE AND CONTENTS OF CONTAINER

ALPHAGAN® P 1.5 (brimonidine tartrate ophthalmic solution) 0.15% sterile solution is supplied in plastic dropper bottles. Each bottle has a fill volume of 5mL.

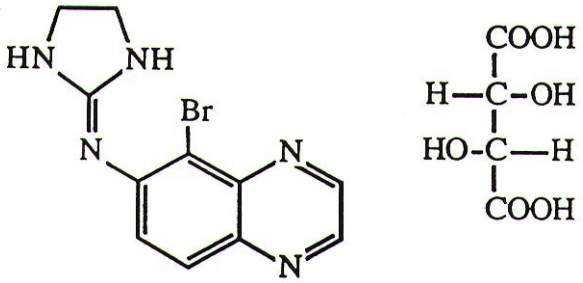
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

Discard contents 4 weeks after opening the bottle.

6.7 PHYSICOCHEMICAL PROPERTIES

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 structure



(Structure of brimonidine tartrate)

Chemical name: 5-bromo-6-(2-imidazolidinylideneamino) quinoxaline L-tartrate.
Molecular weight: 442.24 as the tartrate salt.
Empirical formula: $C_{11}H_{10}BrN_5$, $C_4H_6O_6$

CAS number: 79570-19-7

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 – Prescription Only Medicine
AUST R 158888

8 SPONSOR

Allergan Australia Pty Ltd
810 Pacific Highway
Gordon NSW 2072
A.C.N.: 000 612 831

9 DATE OF FIRST APPROVAL

25 May 2010

10 DATE OF REVISION

19 January 2021

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SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
All	The PI has been reformatted in line with the TGA's approved form for PIs.