NEW ZEALAND DATA SHEET

1. PRODUCT NAME

ALPHAGAN® P 0.15% eye drops

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL of ALPHAGAN® P 1.5 eye drops contains 1.5 mg brimonidine

tartrate, equivalent to 0.99mg as brimonidine free base.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Sterile ophthalmic solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ALPHAGAN® P 1.5 eye drops are effective for lowering intraocular pressure in patients with chronic open-angle glaucoma or ocular hypertension.

4.2 Dosage 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.

Paediatric Use
Safety and effectiveness of ALPHAGAN® P 1.5 eye drops in children has not been established, however 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 oral ingestion. Also see 4.3 Contraindications section.

Use in Patients with Renal or Hepatic Disease
ALPHAGAN® P 1.5 eye drops have not been studied in patients with hepatic or renal impairment (see 4.4 Special warnings and precautions for use).

4.3 Contraindications

ALPHAGAN® P 1.5 eye drops are contraindicated in patients with hypersensitivity to brimonidine tartrate or any of the excipients listed in section 6.1. ALPHAGAN® P 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

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 (see Paediatric Use).

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 eye drops 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.

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

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.

Carcinogenesis, mutagenesis and 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 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.

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.

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).

ALPHAGAN® P 1.5 eye drops are the only IOP-lowering product preserved with Purite®. *In vitro* and *in vivo* studies demonstrate a lower rate of corneal epithelial cytotoxicity (an indicator of ocular surface health) and increased cell viability for Purite®-preserved ophthalmic solutions compared to use of other preservatives.

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.

4.5 Interactions with other medicines and other forms of interaction

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 concomitant drugs such as beta-blockers (ophthalmic and systemic), anti-hypertensives 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 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

Pregnancy

Pregnancy Category B3

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

Breast-feeding

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, ALPHAGAN® P 1.5 eye drops 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. The patient should wait until these symptoms have cleared before driving or using machinery.

4.8 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, eye irritation, blepharitis, eye pain), eye dryness, epiphora, photophobia, superficial punctate keratitis, visual disturbance, visual acuity worsened
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.

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 of suspected adverse reactions:
Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/.

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.

Contact the New Zealand National Poisons Information Centre (telephone 0800 POISON or 0800 764 766) for advice on overdose management.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Brimonidine tartrate is an off-white to pale yellow powder and is both soluble in water (1.5mg/mL) and the product vehicle (3.0 mg/mL) at pH 7.2.

Pharmacotherapeutic group: Sympathomimetics in glaucoma therapy
ATC code: S01EA05

Mechanism of action
Brimonidine is an alpha-2 adrenergic agonist that is 1000-fold more selective for the alpha-2 adrenoreceptor than the alpha-1 adrenoreceptor. Affinity 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 decreases intraocular pressure (IOP) in humans. When used as directed, brimonidine has the action of reducing elevated IOP with minimal effect on cardiovascular parameters.

Pharmacodynamic effects

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

Fluoro photometric 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 efficacy and safety

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® P 1.5 eye drops have the action of lowering IOP with minimal effect on cardiovascular and pulmonary parameters.

ALPHAGAN® P 1.5 eye drops were developed based on the clinical efficacy and tolerability of ALPHAGAN® eye drops. ALPHAGAN® eye drops contain brimonidine tartrate 0.2% and are preserved with benzalkonium chloride. ALPHAGAN® P 1.5eye drops contain brimonidine tartrate 0.15%, are formulated to a physiological pH, contain key electrolytes present in tears (sodium, potassium, calcium, magnesium) and are preserved with Purite®. Data indicate that the substitution of benzalkonium chloride with Purite® decreases the risk of corneal disruption and inflammation, particularly when administered in higher doses (e.g. use of multiple eye drops) and/or chronically. Furthermore, based on non-clinical pharmacokinetic data, Purite® increases the pH and thus enhances the ocular penetration of brimonidine, effectively reducing IOP with lower concentrations of active ingredient, further reducing the potential for adverse reactions. This is confirmed by clinical trials comparing ALPHAGAN® eye drops with ALPHAGAN® P 1.5 eye drops (see Studies with ALPHAGAN® P 1.5 eye drops below).

Studies with ALPHAGAN® eye drops

The long-term efficacy of ALPHAGAN® eye drops was demonstrated in two multicentre studies, one of 12 months and the other of 6 months duration, in subjects with glaucoma or ocular hypertension. The IOP lowering effect of ALPHAGAN® eye drops ranged from an overall mean reduction of 4.1 mm Hg at trough to a peak effect of 6.4 mm Hg. These results represent approximately 16% - 26% mean reduction from baseline measurements. IOP decreases were maintained for up to one year; no tachyphylaxis was observed. Eight percent of subjects were discontinued from the studies due to inadequately controlled IOP.

Analyses of the proportion of subjects who exhibited decreases of ≥ 3 mm Hg at two consecutive visits within the first month of treatment were performed. This subgroup represents 66% of subjects. In these subjects, the overall mean reduction of IOP with ALPHAGAN® eye drops ranged from 5.3 mm Hg at trough to a peak effect of 7.2 mm Hg. These results represent approximately 20% - 30% mean reduction from baseline measurements. At the end of one year, greater than 50% of subjects had IOP reductions of ≥5 mm Hg.

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 391 patients with glaucoma or ocular hypertension already controlled with ALPHAGAN® eye drops (study 017). ALPHAGAN® P 1.5 eye drops twice daily was found to provide equivalent efficacy compared to ALPHAGAN® eye drops twice daily with the mean IOP change from baseline between ALPHAGAN® P 1.5 and ALPHAGAN® being no more than 0.79 mm Hg 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 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 randomized to brimonidine 0.15% (ALPHAGAN® P) 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® for allergic conjunctivitis (9.2% vs 14.6%) and oral dryness (5.3% vs 9.4%). Brimonidine-Purite® eye drops were also associated with significantly less adverse reactions than ALPHAGAN® eye drops for allergic conjunctivitis (14.6% vs 15.7%) and oral dryness (9.4% vs 10.4%) demonstrating 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.

Pharmacokinetics properties

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 0.06ng/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. Systemic accumulation is unlikely after twice daily administration of a 0.15% solution given the short elimination half-life of brimonidine.

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 4.4 Special warnings and precautions for use) or in paediatric patients (see 4.3 Contraindications and 4.2 Dosage and method of administration).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

PRESERVATIVE: sodium chlorite (as Purite®) (stabilized oxychloro complex, solution)

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

Not applicable

6.3 Shelf life:

18 months

6.4 Special precautions for storage:

Store below 25°C

Discard contents 4 weeks after opening the bottle.

6.5 Nature and contents of container

ALPHAGAN® P 1.5 eye drops are a clear, greenish-yellow, sterile ophthalmic solution. ALPHAGAN® P 1.5 eye drops are supplied in opaque plastic dropper bottles (5 mL).

6.6 Special precautions for disposal

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

NEW ZEALAND DATA SHEET

Allergan New Zealand Limited
Corner Manu Tapu Drive and Joseph Hammond Place
Auckland International Airport
Mangere, Auckland
NEW ZEALAND
Toll free telephone: 0800 659 912

9. DATE OF FIRST APPROVAL

November 2006

10. DATE OF REVISION OF THE TEXT

April 2019

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SUMMARY TABLE OF CHANGES

Sections changed	Summary of new information
All headings amended to align to Medsafe's updated DS requirements and sections within the Data Sheet have been moved under the appropriate headings in line with Medsafe's updated DS requirements.	
Minor editorial changes, including typographical and grammatical amendments, implemented throughout the DS to ensure legibility of this document.	
4.3 Amended the contraindication relating to hypersensitivity in line with Medsafe's requirements.	
4.8 Addition of information relating to "Reporting of suspected adverse reactions" in line with Medsafe's updated DS requirements.	
5.1 Addition of Pharmacotherapeutic group in line with Medsafe's updated DS requirements.	
6.2 Additional information included in line with Medsafe's updated DS requirements.	
6.6 Additional information included in line with Medsafe's updated DS requirements	
9 Addition of Date of First Approval of ALPHAGAN® in line with Medsafe's updated DS requirements.	