NEW ZEALAND DATA SHEET

1. PRODUCT NAME

ALPHAGAN® 0.2% eye drops

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL of ALPHAGAN® eye drops contains 2.0 mg brimonidine tartrate, equivalent to 1.32 mg 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® 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® 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® eye drops.

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

Paediatric Use

Symptoms of bradycardia, coma hypotension, lethargy, pallor, respiratory, depression, somnolence, hypothermia, hypotonia and apnea 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.

4.3 Contraindications

ALPHAGAN® eye drops are contraindicated in patients with hypersensitivity to brimonidine tartrate or any of the excipients listed in section 6.1. ALPHAGAN® is also contraindicated in patients receiving monoamine oxidase (MAO) inhibitor therapy.

ALPHAGAN® eye drops are also contraindicated in neonates and infants (children under the age of 2 years)

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

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

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

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.

The preservative in brimonidine eye drops, benzalkonium chloride, may be absorbed by and cause discoloration of soft contact lenses. Patients wearing soft contact lenses should be instructed to remove lenses before administering ALPHAGAN® eye drops and wait at least 15 minutes after using ALPHAGAN® eye drops to re-insert lenses.

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 (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® eye drops were not mutagenic or cytogenic in a series of *in vitro* and *in vivo* studies including the Ames tests, host-mediated assay, chromosomal aberration assay in Chinese Hamster Ovary (CHO) cells, cytogenic studies in mice and dominant lethal assay.

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.

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® eye drops, the possibility of an additive or potentiating effect with CNS depressants (alcohol, barbiturates, opiates, sedatives, or anaesthetics) should be considered.

Because ALPHAGAN® 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 (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® eye drops can lead to an interference in IOP lowering effect. No data on the level of circulating catecholamines after ALPHAGAN® 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.

4.6 Fertility, pregnancy and lactation

Pregnancy:
Category B3

Reproduction studies have been performed in rats at oral doses more than 100 times (0.66 mg base/kg) the plasma drug concentration in humans receiving multiple ophthalmic doses and have revealed no evidence of impaired fertility or harm to the foetus due to ALPHAGAN® eye drops. Additionally, teratogenicity studies showed no adverse effects in rats or rabbits when oral doses were administered at approximately 333 and 24 times respectively, the human drug plasma concentrations resulting from multiple ophthalmic doses.

There are no studies of ALPHAGAN® eye drops in pregnant women, however in animal studies, brimonidine crossed the placenta and entered into the foetal circulation to a related extent. ALPHAGAN® eye drops should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the foetus.

Breast-feeding:
It is not known whether brimonidine 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.

4.7 Effects on ability to drive and use machines

As with other alpha-agonists, ALPHAGAN® 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® 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

In clinical studies, most adverse events were usually transient and not commonly of a severity requiring discontinuation of treatment. The most frequently reported adverse events were:

Ocular: ocular hyperemia, burning and stinging, blurring and foreign body sensation.

Systemic: oral dryness, headache, fatigue/drowsiness.

Events occurring in 1-10% of subjects included:

Ocular: ocular pruritis (itching), corneal staining/erosion, photophobia, ocular allergic reaction, ocular dryness, conjunctival follicles, tearing, ocular ache/pain, eyelid erythema, conjunctival blanching, conjunctival edema, eyelid edema, ocular irritation, abnormal vision, blepharitis, conjunctival discharge.

Systemic: upper respiratory symptoms, dizziness, gastrointestinal symptoms, asthenia, abnormal taste, and nasal dryness.

Events occurring infrequently (less than 1%) in subjects included:

Ocular: conjunctival papillae.

Systemic: systemic allergic reaction, depression and palpitations.

Post Marketing Experience

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 ingestion

The following adverse reactions have been identified during post marketing 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

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

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. Symptoms of brimonidine overdose such as apnea, 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.

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

5. PHARMACOLOGICAL PROPERTIES

Brimonidine tartrate is an off-white, pale yellow to pale pink powder and is water soluble (34 mg/mL).

5.1 Pharmacodynamic properties

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

Pharmacodynamic effects

ALPHAGAN® eye drops have 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.

Fluoro photometric studies in animals and humans suggest that brimonidine tartrate has a dual mechanism of action. ALPHAGAN® 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® eye drops have the action of lowering IOP with minimal effect on cardiovascular and pulmonary parameters.

The long-term efficacy of ALPHAGAN® eye drops was demonstrated in two multicentre studies for one year and 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 mmHg at trough to a peak effect of 6.4 mmHg. 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 mmHg 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 mmHg at trough to a peak effect of 7.2 mmHg. 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 mmHg.

5.2 Pharmacokinetic properties

After ocular administration of a 0.2% solution of ALPHAGAN® eye drops twice daily in humans for 10 days, plasma concentrations were low (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.

In humans, systemic metabolism of brimonidine is extensive; brimonidine does not accumulate. 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

PRESERVATIVE: benzalkonium chloride

INACTIVES: polyvinyl alcohol (LIQUIFILM®), sodium chloride, sodium citrate dihydrate, citric acid monohydrate, and purified water. hydrochloric acid and/or sodium hydroxide may be added to adjust pH (6.3-6.5).

6.2 Incompatibilities

Not applicable

6.3 Shelf life:

30 months

6.4 Special precautions for storage

Storage: Store below 25°C

Discard contents 4 weeks after opening the bottle.

6.5 Nature and contents of container

ALPHAGAN® (brimonidine tartrate) 0.2% eye drops are a clear, greenish-yellow, sterile ophthalmic solution supplied in white opaque plastic dropper bottles (5 mL).

6.6 Special precautions for disposal

No special requirements for disposal

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

AbbVie Limited
6th Floor, 156-158 Victoria St
Wellington, 6011
New Zealand

9. DATE OF FIRST APPROVAL

September 1997

10. DATE OF REVISION OF THE TEXT

04 May 2023

SUMMARY TABLE OF CHANGES

Sections changed	Summary of new information
8	Change in sponsor