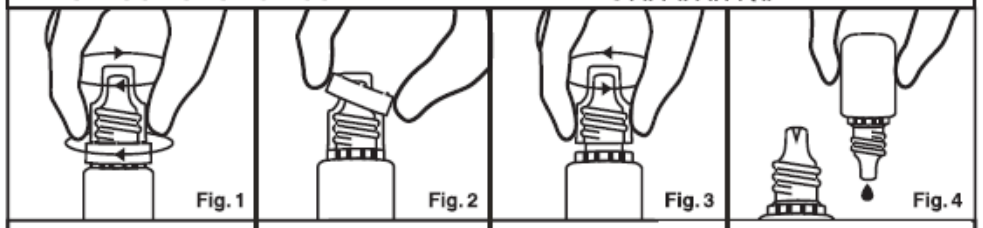
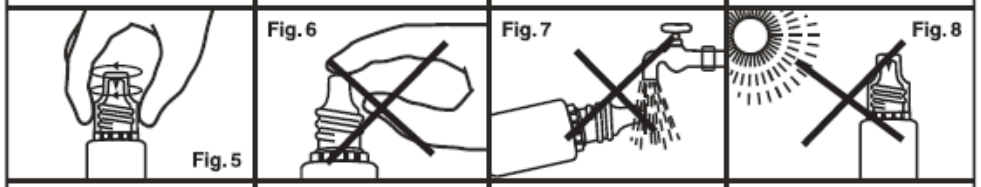
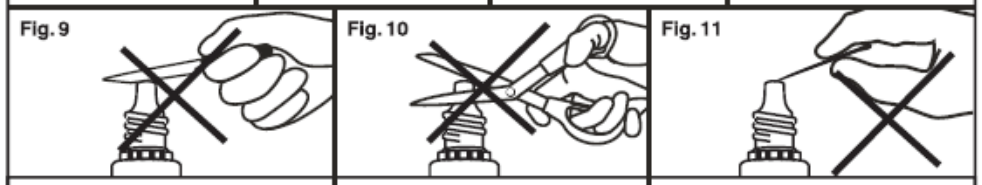
INSTRUCTIONS FOR USE — उपयोग संबंधी निर्देश



Turn right (clockwise) to break the seal and make a dispensing hole on the nozzle	Remove the ring and discard	Open the cap by tuning left (anti-clockwise) and it is ready for use.	Turn it up side down. Squeeze the walls of the bottle gently to deliver sterile drop into the eye.
सिल तोड़ने एवम नोज़ल में छिद्र करने के लिये ढक्कन को दाहने तरफ घुमायें।	छल्ले को निकाल कर फेंक दें।	ढक्कन को खोलने के लिये बांयी तरफ घुमायें। अब बोतल उपयोग के लिये तैयार है।	अब बोतल को उल्टा करें, बोतल की दिवार को हलकेसे दबाएँ और आँखों में दवा की बुंदें डालें।



Replace the cap. Tighten it firmly and keep the bottle closed for subsequent use.	Do not touch the nozzle.	Do not rinse the nozzle.	Do not expose to Sunlight.
पुनः उपयोग में लाने तक ढक्कन को कसकर बोतल वापस बंद कर दें।	बोतल के नोज़ल को हाथ न लगाएँ।	नोज़ल को कभी न धोएँ।	बोतल को धूप में न रखें।



Do not cut with knife	Do not cut with scissor	Do not pierce with needle
चाकु से ना काटें।	कैंची से ना काटें।	सुई से छिद्र न करें।

State of the art technology
From Allergan India Private Limited

अत्याधुनिक तरीके से तैयार किया हुआ
अलरगन इंडिया प्राईवेट लिमिटेड द्वारा

A33/d

For The Use of a Registered Medical Practitioner or a Hospital or a Laboratory Only

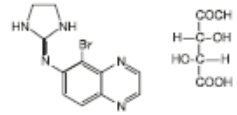
BRIMONIDINE TARTRATE OPHTHALMIC SOLUTION 0.1%

Alphagan® Z

ALLERGAN

DESCRIPTION: ALPHAGAN® Z (brimonidine tartrate ophthalmic solution) is a relatively selective alpha-2 adrenergic agonist for ophthalmic use. The chemical name of brimonidine tartrate is 5-bromo-6-(2-imidazolidinylideneamino) quinoxaline L-tartrate. It is an off-white to pale yellow powder. It has a molecular weight of 442.24 as the tartrate salt, and is both soluble in water (0.6 mg/mL) and in the product vehicle (1.4 mg/mL) at pH 7.7.

The structural formula is



Formula: $C_{11}H_{10}BrN_5 . C_4H_6O_6$

In solution, **ALPHAGAN® Z** (brimonidine tartrate ophthalmic solution 0.1%) has a clear, greenish-yellow color.
It has an osmolality of 250-350 mOsmol/kg and a pH of 7.4-8.0.

Each mL of ALPHAGAN® Z contains:
Brimonidine **Tartrate:** 1mg; (0.1% w/v); Stabilized Oxychloro Complex (Purite™) 0.05 mg (0.005% w.v); Purified Water IP q.s.

Other Excipients: Sodium Carboxy Methyl Cellulose 5 mg (0.5% w/v); Sodium Chloride 5.8mg (0.58% w/v); Potassium Chloride 1.4 mg (0.14% w/v); Calcium Dihydrate Chloride 0.2 mg (0.02% w/v); Magnesium Hexahydrate Chloride 0.06 mg (0.006% w/v)

CLINICAL PHARMACOLOGY: Mechanism of action: ALPHAGAN® Z is an alpha adrenergic receptor agonist. It has a peak ocular hypotensive effect occurring at two hours post-dosing. Fluorophotometric studies in animals and humans suggest that brimonidine tartrate has a dual mechanism of action by reducing aqueous humor production and increasing uveoscleral outflow. **Pharmacokinetics:** After ocular administration of either a 0.1% or 0.2% solution, plasma concentrations peaked within 0.5 to 2.5 hours and declined with a systemic half-life of approximately 2 hours. In humans, systemic metabolism of brimonidine is extensive. 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. **Clinical Evaluations:** 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 tartrate has the action of lowering intraocular pressure with minimal effect on cardiovascular and pulmonary parameters. A clinical study was conducted to evaluate the safety, efficacy, and acceptability of **ALPHAGAN® Z** (brimonidine tartrate ophthalmic solution) 0.1% compared with **ALPHAGAN®** (brimonidine tartrate ophthalmic solution) 0.2% administered three-times-daily in patients with open-angle glaucoma or ocular hypertension. The results indicated that **ALPHAGAN® Z** is equivalent in IOP lowering effect to **ALPHAGAN®**, and effectively lowers IOP in patients with open-angle glaucoma or ocular hypertension by approximately 2-6 mmHg.

INDICATIONS AND USAGE: ALPHAGAN® Z is indicated for the lowering of intraocular pressure in patients with open-angle glaucoma or ocular hypertension.

CONTRAINDICATIONS: ALPHAGAN® Z is contraindicated in patients with hypersensitivity to brimonidine tartrate or any component of this medication. It is also contraindicated in patients receiving monoamine oxidase (MAO) inhibitor therapy.

PRECAUTIONS: General: Although brimonidine tartrate ophthalmic solution had minimal effect on the blood pressure of patients in clinical studies, caution should be exercised in treating patients with severe cardiovascular disease. **ALPHAGAN® Z** has not been studied in patients with hepatic or renal impairment; caution should be used in treating such patients. **ALPHAGAN® Z** should be used with caution in patients with depression, cerebral or coronary insufficiency, Raynaud's phenomenon, orthostatic hypotension, or thromboangiitis obliterans. Patients prescribed IOP-lowering medication should be routinely monitored for IOP. **Information for Patients:** As with other drugs in this class, **ALPHAGAN® Z** may cause fatigue and /or drowsiness in some patients. Patients who engage in hazardous activities 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® Z**, the possibility of an additive or potentiating effect with CNS depressants (alcohol, barbiturates, opiates, sedatives, or anesthetics) should be considered. Alpha-agonists, as a class, may reduce pulse and blood pressure. Caution in using concomitant drugs such as anti-hypertensives and/or cardiac glycosides is advised. 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® Z** in humans can lead to resulting interference with the IOP lowering effect. No data on the level of circulating catecholamines after **ALPHAGAN® Z** administration are available. Caution, however, is advised in patients taking tricyclic antidepressants which can affect the metabolism and uptake of circulating amines. **Carcinogenesis, Mutagenesis, and Impairment of Fertility:** No compound-related carcinogenic effects were observed in either mice or rats following a 21-month and 24-month study, respectively. In these studies, dietary administration of brimonidine tartrate at doses up to 2.5 mg/kg/day in mice and 1.0 mg/kg/day in rats achieved 150 and 120 times or 90 and 80 times, respectively, the plasma drug concentration (Cmax) estimated in humans treated with one drop of **ALPHAGAN® Z** into both eyes 3 times per day. Brimonidine tartrate was not mutagenic or cytogenic in a series of in vitro and in vivo studies including the Ames test, chromosomal aberration assay in Chinese Hamster Ovary (CHO) cells, a host-mediated assay and cytogenic studies in mice, and dominant lethal assay.

Pregnancy: Teratogenic effects: Pregnancy Category B. Reproductive studies performed in rats and rabbits with oral doses of 0.66 mg base/kg revealed no evidence of impaired fertility or harm to the fetus due to **ALPHAGAN® Z**. Dosing at this level produced an exposure in rats and rabbits that is 190 and 100 times or 120 and 60 times higher, respectively, than the exposure seen in humans following multiple ophthalmic doses of **ALPHAGAN® Z.** There are no adequate and well-controlled studies in pregnant women. In animal studies, brimonidine crossed the placenta and entered into the fetal circulation to a limited extent. **ALPHAGAN® Z** should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus. **Nursing Mothers:** It is not known whether this drug is excreted in human milk; although in animal studies brimonidine tartrate was 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.

Pediatric Use: In a well-controlled clinical study conducted in pediatric glaucoma patients (ages 2 to 7 years) the most commonly observed adverse events with brimonidine tartrate ophthalmic solution 0.2% dosed three times daily were somnolence (50%-83% in patients ages 2 to 6 years) and decreased alertness. In pediatric patients 7 years of age or older (>20kg), somnolence appears to occur less frequently (25%). Approximately 16% of patients on brimonidine tartrate ophthalmic solution discontinued from the study due to somnolence. The safety and effectiveness of brimonidine tartrate ophthalmic solution have not been studied in pediatric patients below the age of 2 years. Brimonidine tartrate ophthalmic solution is not recommended for use in pediatric patients under the age of 2 years

Geriatric Use: No overall differences in safety or effectiveness have been observed between elderly and other adult patients.

ADVERSE REACTIONS: Adverse events occurring in approximately 10-20% of the subjects receiving brimonidine ophthalmic solution (0.1-0.2%) included: allergic conjunctivitis, conjunctival hyperemia, and eye pruritus. Adverse events occurring in approximately 5-9% included: burning sensation, conjunctival folliculosis, hypertension, ocular allergic reaction, oral dryness, and visual disturbance. Adverse events occurring in approximately 1-4% of the subjects receiving brimonidine ophthalmic solution (0.1-0.2%) included: allergic reaction, asthenia, blepharitis, blepharoconjunctivitis, blurred vision, bronchitis, cataract, conjunctival edema, conjunctival hemorrhage, conjunctivitis, cough, dizziness, dyspepsia, dyspnea, epiphora, eye discharge, eye dryness, eye irritation, eye pain, eyelid edema, eyelid erythema, fatigue, flu syndrome, follicular conjunctivitis, foreign body sensation, gastrointestinal disorder, headache, hypercholesterolemia, hypotension, infection (primarily colds and respiratory infections), insomnia, keratitis, lid disorder, pharyngitis, photophobia, rash, rhinitis, sinus infection, sinusitis, somnolence, stinging, superficial punctate keratopathy, tearing, visual field defect, vitreous detachment, vitreous disorder, vitreous floaters, and worsened visual acuity. The following events were reported in less than 1% of subjects: corneal erosion, hordeolum, nasal dryness, and taste perversion. The following events have been identified during post-marketing use of brimonidine tartrate ophthalmic solutions in clinical practice. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. The events, which have been chosen for inclusion due to either their seriousness, frequency of reporting, possible causal connection to brimonidine tartrate ophthalmic solutions, or a combination of these factors, include: bradycardia; depression; iritis; keratoconjunctivitis sicca; miosis; nausea; skin reactions (including erythema, eyelid pruritus, rash, and vasodilation) and tachycardia. Apnea; bradycardia; hypotension; hypothermia; hypotonia; and somnolence have been reported in infants receiving brimonidine tartrate ophthalmic solutions.

OVERDOSAGE: No information is available on overdosage in humans. Treatment of an oral overdose includes supportive and symptomatic therapy; a patent airway should be maintained.

DOSAGE AND ADMINISTRATION: The recommended dose is one drop of **ALPHAGAN® Z** in the affected eye(s) three times daily, approximately 8 hours apart. **ALPHAGAN® Z** ophthalmic solution may be used concomitantly with other topical ophthalmic drug products to lower intraocular pressure. If more than one topical ophthalmic product is being used, the products should be administered at least 5 minutes apart.

HOW SUPPLIED: ALPHAGAN® Z is supplied sterile in opaque teal plastic dropper bottles.
Store in cool and dark place. Use the solution within one month after opening the container.
MEDICINE: Keep out of reach of children.

Marketed by:
Allergan India Private Limited;

Manufactured in India by: Piramal Healthcare Ltd., Plot No. 67-70, Sector 2, Pithampur – 454 775, Dist. Dhar, Madhya Pradesh

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