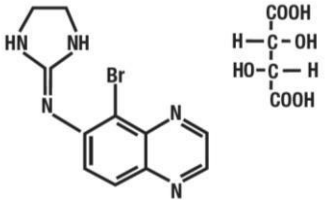
BRIMONIDINE
tartrate

2 mg/mL (0.2%)
Sterile Ophthalmic Solution
Antiglaucoma and Miotic

DESCRIPTION:
BRIMONIDINE tartrate 2 mg/mL (0.2%) Sterile 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 has a molecular weight of 442.24 as the tartrate salt and is water soluble (34 mg/mL) at pH 6.5. The structural formula is



Formula: $C_{11}H_{10}BrN_5 \cdot C_4H_6O_6$
CAS Number 59803-98-4

In solution, BRIMONIDINE tartrate 2 mg/mL (0.2%) Sterile Ophthalmic Solution has a clear, greenish-yellow color. It has an osmolality of 280-330 mOsml/kg and a pH of 5.6-6.6.

FORMULATION:
Active: 1 ml solution contains 2 mg brimonidine tartrate
Preservative: benzalkonium chloride
Excipients: Citric acid; polyvinyl alcohol; sodium chloride; sodium citrate; purified water. Hydrochloric acid and/or sodium hydroxide may be added to adjust pH.

CLINICAL PHARMACOLOGY

Mechanism of action:
BRIMONIDINE tartrate 2 mg/mL (0.2%) Sterile Ophthalmic Solution 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 a 0.2% solution, 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. 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.

In comparative clinical studies with timolol 0.5%, lasting up to one year, the IOP lowering effect of brimonidine tartrate was approximately 4-6 mm Hg compared with approximately 6 mm Hg for timolol. In these studies, both patient groups were dosed BID; however, due to the duration of action of BRIMONIDINE tartrate 2 mg/mL (0.2%) Sterile Ophthalmic Solution, it is recommended that BRIMONIDINE tartrate 2 mg/mL (0.2%) Sterile Ophthalmic Solution be dosed TID. Eight percent of subjects were discontinued from studies due to inadequately controlled intraocular pressure, which in 30% of these patients occurred during the first month of therapy. Approximately 20% were discontinued due to adverse experiences.

INDICATIONS AND USAGE
BRIMONIDINE tartrate 2 mg/mL (0.2%) Sterile Ophthalmic Solution is indicated for lowering intraocular pressure in patients with open-angle glaucoma or ocular hypertension. The IOP lowering efficacy of BRIMONIDINE tartrate 2 mg/mL (0.2%) Sterile Ophthalmic Solution diminishes over time in some patients. This loss of effect appears with a variable time of onset in each patient and should be closely monitored.

CONTRAINDICATIONS
- Hypersensitivity to the active substance or to any of the excipients.
- Patients receiving monoamine oxidase (MAO) inhibitor therapy.
- Neonates and infants younger than 2 years old

PRECAUTIONS
General:
Although BRIMONIDINE tartrate 2 mg/mL (0.2%) Sterile Ophthalmic Solution has a minimal effect on blood pressure of patients in clinical studies, caution should be taken in treating patients with severe cardiovascular disorders.

BRIMONIDINE tartrate 2 mg/mL (0.2%) Sterile Ophthalmic Solution has not been studied in patients with hepatic or renal impairment; caution should be used in treating such patients. BRIMONIDINE tartrate 2 mg/mL (0.2%) Sterile Ophthalmic Solution should be used with caution in patients with depression, cerebrovascular or coronary insufficiency, Raynaud's disease, orthostatic hypotension or thromboangiitis obliterans.

Brimonidine tartrate may cause ocular allergic reactions. If allergic reactions are observed, treatment should be discontinued.

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

Information for Patients:
BRIMONIDINE tartrate 2 mg/mL (0.2%) Sterile Ophthalmic Solution contains benzalkonium chloride which may cause eye irritation and is known to discolour soft contact lenses. Avoid contact with soft contact lenses. Patients must be instructed to remove contact lenses prior to application of BRIMONIDINE tartrate 2 mg/mL (0.2%) Sterile Ophthalmic Solution and wait at least 15 minutes before reinsertion.

As with other drugs in this class, BRIMONIDINE tartrate 2 mg/mL (0.2%) Sterile Ophthalmic Solution 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.

Interaction with other medicinal products and other forms of interaction
Although specific drug interaction studies have not been conducted with BRIMONIDINE tartrate 2 mg/mL (0.2%) Sterile Ophthalmic Solution, the possibility of an additive or potentiating effect with CNS depressants (alcohol, barbiturates, opiates, sedatives, or anesthetics) should be considered.

BRIMONIDINE tartrate 2 mg/mL (0.2%) Sterile Ophthalmic Solution is contraindicated in patients receiving monoamine oxidase inhibitors.

Alpha agonists, as a class, may reduce pulse and blood pressure. Caution is advised with concomitant use of drugs such as antihypertensive and/or cardiac glycosides with similar cardiovascular effects (drugs that cause hypotension).

Caution is advised in patients on antidepressants which can affect noradrenergic transmission (e.g. tricyclic antidepressants and miaserin). In addition, 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 BRIMONIDINE tartrate 2 mg/mL (0.2%) Sterile Ophthalmic Solution in humans can lead to resulting interference with the IOP lowering effect. No data on the level of circulating catecholamines after BRIMONIDINE tartrate 2 mg/mL (0.2%) Sterile Ophthalmic Solution are available. Caution, however, is advised in patients taking medications which can affect the metabolism and uptake of circulating amines e.g. chlorpromazine, methylphenidate, reserpine, as these agents may blunt the hypotensive response.

The possibility of an additive or potentiating effect with CNS depressants (e.g., alcohol, barbiturates, opiates, sedatives or anesthetics) should be considered.

Caution is advised when initiating (or changing the dose of) a concomitant systemic agent (irrespective of pharmaceutical form) which may interact with α-adrenergic agonists or interfere with their activity i.e. agonists or antagonists of the adrenergic receptor e.g. (isoprenaline, prazosin).

Carcinogenesis, mutagenesis, 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 ~77 and 118 times, respectively, the plasma drug concentration estimated in humans treated with one drop BRIMONIDINE tartrate 2 mg/mL (0.2%) Sterile Ophthalmic solution 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.

Reproductive studies performed in rats with oral doses of 0.66 mg base/kg revealed no evidence of harm to the fetus due to BRIMONIDINE tartrate 2 mg/mL (0.2%) Sterile Ophthalmic Solution.

Studies have not been performed to evaluate the effects of topical ocular administration of brimonidine on fertility.

Pregnancy: Teratogenic Effects: Pregnancy Category B.
Reproduction studies performed in rats with oral doses of 0.66 mg base/kg revealed no evidence of harm to the fetus due to Brimonidine tartrate 2mg/mL (0.2%) Sterile Ophthalmic Solution. Dosing at this level produced 100 times the plasma drug concentration level seen in humans following multiple ophthalmic doses.

There are no or limited amount of data from the use of topical brimonidine in pregnant women. Animal studies with brimonidine at concentrations relevant to the maximum human exposure do not indicate direct harmful effects with respect to reproductive toxicity. In animal studies, brimonidine crossed the placenta and entered into the fetal circulation to a limited extent. BRIMONIDINE tartrate 2 mg/mL (0.2%) Sterile Ophthalmic Solution should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus.

Lactation:
It is unknown whether topical brimonidine is excreted in human milk; however, a risk to the suckling child cannot be excluded. In animal studies, brimonidine administered orally 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 population
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 2mg/mL (0.2%) Sterile Ophthalmic Solution 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%). The most commonly observed adverse event was somnolence. Approximately 16% of patients on Brimonidine tartrate ophthalmic solution discontinued from the study due to somnolence.
The safety and effectiveness of BRIMONIDINE tartrate 2 mg/mL (0.2%) Sterile Ophthalmic Solution have not been studied in pediatric patients below the age of 2 years. BRIMONIDINE tartrate 2 mg/mL (0.2%) Sterile Ophthalmic Solution is not recommended for use in pediatric patients under the age of 2 years.

Brimonidine is not recommended in children older than 2 years because of the potential for CNS depression.

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

UNDESIRABLE EFFECTS
The following adverse reactions have been reported during clinical studies and post-marketing experience with BRIMONIDINE tartrate 2 mg/mL (0.2%) Sterile Ophthalmic Solution and are classified according to the subsequent convention: very common (≥ 1/10), common (≥ 1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000) and very rare (<1/10,000). Within each frequency-grouping, adverse reactions are presented in order of decreasing seriousness.

System Organ	**MedDRA Preferred Term (v. 16.1)**
Infections and infestations	*Uncommon*: pharyngitis
Immune system disorders	*Common*: hypersensitivity *Rare*: seasonal allergy
Nervous system disorders	*Uncommon*: dizziness, somnolence, headache
Eye disorders	*Common:* conjunctivitis, conjunctivitis allergic, conjunctival follicles, vision blurred, ocular discomfort, eye pruritus, dry eye, ocular hyperemia *Uncommon:* punctate keratitis, visual acuity reduced, blepharitis, photophobia, eye pain, lacrimation increased, eye discharge, eye allergy, erythema of eyelid *Rare:* lacrimation decreased, eyelid edema
Respiratory, thoracic and mediastinal disorders	*Uncommon*: upper-airway cough syndrome *Rare*: dysphonia, cough, nasal congestion, dry throat, nasal dryness
Gastrointestinal disorders	*Common*: dry mouth *Uncommon*: nausea, dysgeusia
Skin and subcutaneous tissue disorders	*Uncommon*: dermatitis allergic
General disorders and administration site conditions	*Uncommon:* fatigue, thirst
Vascular disorders	*Rare:* blood pressure diastolic increased, blood pressure systolic decreased

Additional adverse reactions with BRIMONIDINE tartrate 2 mg/mL (0.2%) Sterile Ophthalmic Solution identified from post-marketing surveillance include the following. Frequencies cannot be estimated from the available data. Within each System Organ Class adverse reactions are presented in order of decreasing seriousness.

System Organ Classification	MedDRA Preferred Term (v. 16.1)
Eye disorders	Iridocyclitis, miosis
Cardiac disorders	Bradycardia, tachycardia
Respiratory, thoracic and mediastinal disorders	dyspnea
Skin and subcutaneous tissue disorders	Erythema, pruritus, rash

Pediatric population

Brimonidine is contraindicated in neonates and infants younger than 2 years old and not recommended in children older than 2 years because of the potential for CNS depression.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

BRIMONIDINE tartrate 2 mg/mL (0.2%) Sterile Ophthalmic Solution may cause fatigue, and somnolence in some patients. Patients who engage in hazardous activities should be cautioned of the potential for a decrease in mental alertness.

OVERDOSE

Systemic overdose resulting from accidental ingestion (Adults):

There is very limited information regarding accidental ingestion of brimonidine in adults. Treatment of an oral overdose includes supportive and symptomatic therapy; patient's airway should be maintained.

Oral overdoses of other alpha-2-agonists have been reported to cause symptoms such as hypotension, asthenia, vomiting, lethargy, sedation, bradycardia, arrhythmias, miosis, apnea, hypotonia, hypothermia, respiratory depression and seizure.

Pediatric population

Reports of serious adverse effects following inadvertent ingestion of the product by pediatric subjects have been published or reported to the product. The subjects experienced symptoms of CNS depression, typically temporary coma or low level of consciousness, lethargy, somnolence, hypotonia, bradycardia, hypothermia, pallor, respiratory depression and apnea, and required admission to intensive care with intubation if indicated. All subjects were reported to have made a full recovery, usually within 6-24 hours.

DOSAGE AND ADMINISTRATION

The recommended dose is one drop of BRIMONIDINE tartrate 2 mg/mL (0.2%) Sterile Ophthalmic Solution in the affected eye(s) three times daily, approximately 8 hours apart. BRIMONIDINE tartrate 2 mg/mL (0.2%) Sterile 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.

AVAILABILITY:
BRIMONIDINE tartrate 2 mg/mL (0.2%) Sterile Ophthalmic Solution is supplied as 5 mL in white opaque LDPE plastic droptainer bottle with tip, and with purple polypropylene cap.

STORAGE:
Store at temperatures not exceeding 25°C.

CAUTION: Foods, Drugs, Devices, and Cosmetics Act prohibits dispensing without prescription.

For suspected adverse drug reaction, report to the FDA: www.fda.gov.ph
The patient is advised to seek IMMEDIATE medical attention at the first sign of adverse drug reaction.

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NOVARTIS

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