# BRIMONIDINE TARTRATE- brimonidine tartrate solution
# Sandoz Inc

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**HIGHLIGHTS OF PRESCRIBING INFORMATION**
**These highlights do not include all the information needed to use BRIMONIDINE TARTRATE OPHTHALMIC SOLUTION safely and effectively. See full prescribing information for BRIMONIDINE TARTRATE OPHTHALMIC SOLUTION.**

**BRIMONIDINE TARTRATE ophthalmic solution, for ophthalmic use**
**Initial U.S. Approval: 1996**

## INDICATIONS AND USAGE

Brimonidine tartrate ophthalmic solution, 0.15% is an alpha-2 adrenergic receptor agonist indicated for the lowering of intraocular pressure in patients with open-angle glaucoma or ocular hypertension (1).

## DOSAGE AND ADMINISTRATION

- Instill one drop in the affected eye(s) three-times daily (2).
- If more than one topical ophthalmic product is being used, the products should be administered at least 5 minutes apart (2).

## DOSAGE FORMS AND STRENGTHS

Solution containing 1.5 mg/mL brimonidine tartrate (3)

## CONTRAINDICATIONS

- Hypersensitivity to any component of this product (4.1).

## WARNINGS AND PRECAUTIONS

- Potentiation of vascular insufficiency (5.1)

## ADVERSE REACTIONS

Most common adverse reactions are allergic conjunctivitis, conjunctival hyperemia, and eye pruritis (6.1).
**To report SUSPECTED ADVERSE REACTIONS, contact Sandoz Inc. at 1-800-525-8747 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.**

## DRUG INTERACTIONS

- Concomitant use with systemic beta-blockers may potentiate systemic beta-blockade (7.1).
- Use with CNS depressants may result in an additive or potentiating effect (7.2).
- Tricyclic antidepressants may potentially blunt the hypotensive effect of systemic clonidine (7.3).
- Monoamine oxidase inhibitors may result in increased hypotension (7.4).

## USE IN SPECIFIC POPULATIONS

- Not for use in children below the age of 2 years (8.4).

**See 17 for PATIENT COUNSELING INFORMATION.**

**Revised: 5/2021**

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## FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

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## FULL PRESCRIBING INFORMATION

### 1 INDICATIONS AND USAGE

Brimonidine tartrate ophthalmic solution, 0.15% is indicated for the lowering of intraocular pressure in patients with open-angle glaucoma or ocular hypertension.

### 2 DOSAGE AND ADMINISTRATION

The recommended dose is one drop of brimonidine tartrate ophthalmic solution, 0.15% in the affected eye(s) three-times daily, approximately 8 hours apart.

Brimonidine tartrate ophthalmic solution, 0.15% 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.

## 3 DOSAGE FORMS AND STRENGTHS

Brimonidine tartrate ophthalmic solution, 1.5 mg/mL.

## 4 CONTRAINDICATIONS

### 4.1 Hypersensitivity

Brimonidine tartrate ophthalmic solution, 0.15% is contraindicated in patients with hypersensitivity to any component of this product.

## 5 WARNINGS AND PRECAUTIONS

### 5.1 Potentiation of Vascular Insufficiency

Brimonidine tartrate ophthalmic solution, 0.15% may potentiate syndromes associated with vascular insufficiency. Brimonidine tartrate ophthalmic solution, 0.15% should be used with caution in patients with depression, cerebral or coronary insufficiency, Raynaud's phenomenon, orthostatic hypotension, or thromboangiitis obliterans.

## 6 ADVERSE REACTIONS

### 6.1 Clinical Studies Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Adverse events occurring in approximately 10-20% of the subjects included: allergic conjunctivitis, conjunctival hyperemia, and eye pruritis.

Adverse events occurring in approximately 5-9% of the subjects included: burning sensation, conjunctival folliculosis, hypertension, ocular allergic reaction, oral dryness, and visual disturbance.

Events occurring in approximately 1-4% of subjects included: allergic reaction, arthralgia, arthritis, asthenia, blepharitis, blepharoconjunctivitis, blurred vision, bronchitis, cataract, chest pain, conjunctival edema, conjunctival hemorrhage, conjunctivitis, cough, dizziness, diabetes mellitus, 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, insomnia, joint disorder, keratitis, lid disorder, osteoporosis, 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, nasal dryness, and taste perversion.

### 6.2 Postmarketing Experience

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, iritis, miosis, skin reactions (including erythema, eyelid pruritis, rash, and vasodilation), and tachycardia. Apnea, bradycardia, hypotension, hypothermia, hypotonia, and somnolence have been reported in infants receiving brimonidine tartrate ophthalmic solutions.

## 7 DRUG INTERACTIONS

### 7.1 Anti-hypertensives / Cardiac Glycosides

Alpha-2 agonists, as a class, may reduce blood pressure. Caution in using drugs such as beta-blockers (ophthalmic and systemic), anti-hypertensives and/or cardiac glycosides is advised.

### 7.2 CNS Depressants

Although specific drug interaction studies have not been conducted with brimonidine tartrate ophthalmic solution, 0.15%, the possibility of an additive or potentiating effect with CNS depressants (alcohol, barbiturates, opiates, sedatives, or anesthetics) should be considered.

### 7.3 Tricyclic Antidepressants

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 ophthalmic solution, 0.15% in humans can lead to resulting interference with its IOP-lowering effect. Caution, however, is advised in patients taking tricyclic antidepressants, which can affect the metabolism and uptake of circulating amines.

### 7.4 Monoamine Oxidase Inhibitors

Monoamine oxidase (MAO) inhibitors may theoretically interfere with the metabolism of brimonidine and potentially result in an increased systemic side-effect such as hypotension. Caution is advised in patients taking MAO inhibitors which can affect the metabolism and uptake of circulating amines.

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

Reproductive studies performed in rats and rabbits with oral doses of 0.66 mg base/kg revealed no evidence of harm to the fetus due to brimonidine tartrate ophthalmic solution, 0.15%. Dosing at this level produced an exposure in rats and rabbits that is 80 and 40 times higher than the exposure seen in humans, respectively.

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. Brimonidine tartrate ophthalmic solution, 0.15% should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus.

### 8.3 Nursing Mothers

It is not known whether this drug is excreted in human milk. 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.

### 8.4 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 (>20 kg), 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.

### 8.5 Geriatric Use

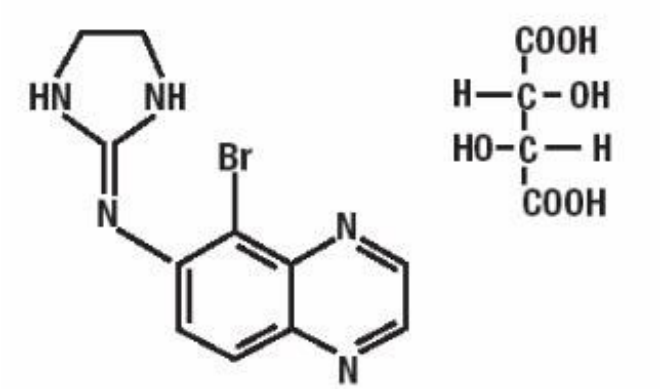
No overall differences in safety or effectiveness have been observed between elderly and other adult patients.

## 10 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.

## 11 DESCRIPTION

Brimonidine tartrate ophthalmic solution, 0.15% (1.5 mg brimonidine tartrate per mL equivalent to 1.0 mg brimonidine free base per mL) 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 (1.5 mg/mL) and in the product vehicle (3.0 mg/mL) at pH 7.2. The structural formula is:



Formula: $C_{11}H_{10}BrN_5 \bullet C_4H_6O_6$

CAS Number: 59803-98-4

In solution, brimonidine tartrate ophthalmic solution, 0.15% has a clear, greenish-yellow color. It has an osmolality of 250 - 350 mOsmol/kg and a pH of 6.6 - 7.4.

Contains: **Active ingredient:** brimonidine tartrate 1.5 mg/mL, **Preservative:** POLYQUAD* 0.01 mg/mL, **Inactives:** povidone, boric acid, sodium borate, calcium chloride, magnesium chloride, potassium chloride, mannitol, sodium chloride, purified water, with hydrochloric acid and/or sodium hydroxide to adjust pH.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

Brimonidine tartrate ophthalmic solution, 0.15% is an alpha-2 adrenergic receptor agonist. 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.

### 12.2 Pharmacodynamics

Brimonidine tartrate ophthalmic solution, 0.15% has a peak ocular hypotensive effect occurring at two hours post-dosing.

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.

### 12.3 Pharmacokinetics

#### *Absorption*

In a pharmacokinetic study, 14 healthy subjects (4 males and 10 females) received a single topical ocular administration of brimonidine tartrate ophthalmic solution, 0.15%, one drop per eye. The peak plasma concentrations ($C_{max}$) and $AUC_{0\text{-}inf}$ were 73 ± 19 pg/mL and 375 ± 89 pg•hr/mL, respectively. $T_{max}$ was 1.7 ± 0.7 hours after dosing. The systemic half-life was approximately 2.1 hours.

***Metabolism***

Brimonidine is metabolized primarily by the liver. *In vitro* metabolism data from human microsomal fractions and liver slices indicate that brimonidine undergoes extensive hepatic metabolism.

***Excretion***

Urinary excretion is the major route of elimination of brimonidine and its metabolites. Approximately 87% of an orally administered radioactive dose of brimonidine was eliminated within 120 hours, with 74% of the radioactivity recovered in the urine.

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No compound-related carcinogenic effects were observed in either mice or rats following a 21-month and a 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 60 and 50 times, respectively, the plasma drug concentration estimated in humans treated with one drop of brimonidine tartrate ophthalmic solution, 0.15% into both eyes.

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.

## 14 CLINICAL STUDIES

A clinical study was conducted to evaluate the safety and efficacy of brimonidine tartrate ophthalmic solution, 0.15% compared to Alphagan® P** administered three times daily in patients with open-angle glaucoma or ocular hypertension. The results indicated that brimonidine tartrate ophthalmic solution, 0.15% is equivalent in IOP-lowering effect to Alphagan® P (brimonidine tartrate ophthalmic solution), 0.15%, and effectively lowers IOP in patients with open-angle glaucoma or ocular hypertension by 2 - 6 mmHg.

## 16 HOW SUPPLIED/STORAGE AND HANDLING

Brimonidine tartrate ophthalmic solution, 0.15% is supplied sterile in opaque white LDPE plastic bottles and natural tips with purple polypropylene caps as follows:

5 mL in 8 mL bottle NDC 61314-144-05
10 mL in 10 mL bottle NDC 61314-144-10
15 mL in 15 mL bottle NDC 61314-144-15

**Storage:** Store at 15° to 25° C (59° to 77°F).

## 17 PATIENT COUNSELING INFORMATION

As with other drugs in this class, brimonidine tartrate ophthalmic solution, 0.15% 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.

**Rx Only**

*POLYQUAD is a registered trademark of Alcon Research, LLC.

**ALPHAGAN P is a registered trademark of Allergan, Inc.

Manufactured by

Alcon Laboratories, Inc.

Fort Worth, Texas 76134 for

Sandoz Inc.

Princeton, NJ 08540

300042903-0521

**PRINCIPLE DISPLAY PANEL**

**NDC** 61314-144-05

**Brimonidine**

**Tartrate**

**Ophthalmic**

**Solution**

**0.15%**

**Rx Only**

STERILE

5 mL

FOR TOPICAL OPHTHALMIC USE ONLY

SANDOZ


# BRIMONIDINE TARTRATE

brimonidine tartrate solution

| Product Information | | | |
|---|---|---|---|
| **Product Type** | HUMAN PRESCRIPTION DRUG | **Item Code (Source)** | NDC:61314-144 |
| **Route of Administration** | OPHTHALMIC | | |

| Active Ingredient/Active Moiety | | |
|---|---|---|
| **Ingredient Name** | **Basis of Strength** | **Strength** |
| **BRIMONIDINE TARTRATE** (UNII: 4S9CL2DY2H) (BRIMONIDINE - | BRIMONIDINE | 1.5 mg |

| | | |
|---|---|---|
| UNII:E6GNX3HHTE) | TARTRATE | in 1 mL |

## Inactive Ingredients

| Ingredient Name | Strength |
|---|---|
| **POVIDONE, UNSPECIFIED** (UNII: FZ989GH94E) | |
| **BORIC ACID** (UNII: R57ZHV85D4) | |
| **SODIUM BORATE** (UNII: 91MBZ8H3QO) | |
| **CALCIUM CHLORIDE** (UNII: M4I0D6VV5M) | |
| **POTASSIUM CHLORIDE** (UNII: 660YQ98I10) | |
| **MANNITOL** (UNII: 3OWL53L36A) | |
| **SODIUM CHLORIDE** (UNII: 451W47IQ8X) | |
| **WATER** (UNII: 059QF0KO0R) | |
| **HYDROCHLORIC ACID** (UNII: QTT17582CB) | |
| **SODIUM HYDROXIDE** (UNII: 55X04QC32I) | |

## Packaging

| # | Item Code | Package Description | Marketing Start Date | Marketing End Date |
|---|---|---|---|---|
| **1** | NDC:61314-144-05 | 5 mL in 1 BOTTLE; Type 0: Not a Combination Product | 10/02/2010 | |
| **2** | NDC:61314-144-10 | 10 mL in 1 BOTTLE; Type 0: Not a Combination Product | 10/02/2010 | |
| **3** | NDC:61314-144-15 | 15 mL in 1 BOTTLE; Type 0: Not a Combination Product | 10/02/2010 | |

## Marketing Information

| Marketing Category | Application Number or Monograph Citation | Marketing Start Date | Marketing End Date |
|---|---|---|---|
| NDA | NDA021764 | 10/02/2010 | |

## Labeler - Sandoz Inc (005387188)

Revised: 5/2021 Sandoz Inc