

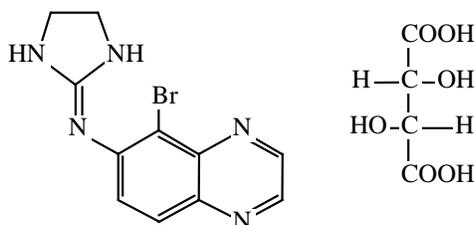
NDA 21-764
Page 3

Brimonidine Tartrate Ophthalmic Solution, 0.15%

Sterile

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: $C_{11}H_{10}BrN_5 \cdot C_4H_6O_6$

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.

Each mL of Brimonidine Tartrate Ophthalmic Solution, 0.15% contains:

Active ingredient: brimonidine tartrate 0.15% (1.5 mg/mL)

Inactives: povidone; boric acid; sodium borate; calcium chloride; magnesium chloride; potassium chloride; mannitol; sodium chloride; POLYQUAD* 0.001% (0.01 mg/mL); purified water; with hydrochloric acid and/or sodium hydroxide to adjust pH.

CLINICAL PHARMACOLOGY

Mechanism of Action:

Brimonidine Tartrate Ophthalmic Solution, 0.15% is an alpha-2 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.

NDA 21-764

Page 4

Pharmacokinetics:

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-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.

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.

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.

Special Populations

Brimonidine Tartrate Ophthalmic Solution, 0.15% has not been studied in patients with hepatic or renal impairment. Because of the low systemic drug exposure following topical ocular administration of Brimonidine Tartrate Ophthalmic Solution, 0.15%, no dose adjustment is necessary when treating patients with hepatic or renal impairment.

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 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 mm Hg.

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.

CONTRAINDICATIONS

Brimonidine Tartrate Ophthalmic Solution, 0.15% 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.

NDA 21-764

Page 5

PRECAUTIONS

General:

Although Brimonidine Tartrate Ophthalmic Solution, 0.15% had minimal effect on the blood pressure of patients in clinical studies, caution should be exercised in treating patients with severe cardiovascular disease.

Brimonidine Tartrate Ophthalmic Solution, 0.15% has not been studied in patients with hepatic or renal impairment; caution should be used in treating such patients.

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. Patients prescribed IOP-lowering medication should be routinely monitored for IOP.

Information for Patients:

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.

Drug Interactions:

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. Alpha-2 agonists, as a class, may reduce pulse and blood pressure. Caution in using concomitant drugs such as beta-blockers (ophthalmic and systemic), 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 Brimonidine Tartrate Ophthalmic Solution, 0.15% in humans can interfere with its IOP-lowering effect. No data on the level of circulating catecholamines after Brimonidine Tartrate Ophthalmic Solution, 0.15% 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 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.

NDA 21-764

Page 6

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 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.

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.

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. (Also refer to **ADVERSE REACTIONS** section.)

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 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.

NDA 21-764
Page 7

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.

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.

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 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.

HOW SUPPLIED

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°-25° C (59° - 77°F).

Rx Only

NDA 21-764

Page 8

Distributed by:
Falcon Pharmaceuticals
Fort Worth, Texas 76134

Manufactured by:
Alcon Manufacturing, Ltd.
Fort Worth, Texas 76134
Printed in USA

*POLYQUAD is a registered trademark of Alcon Manufacturing, Ltd.

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

Carton Label

5 mL



NDA 21-764

Page 9

10 mL



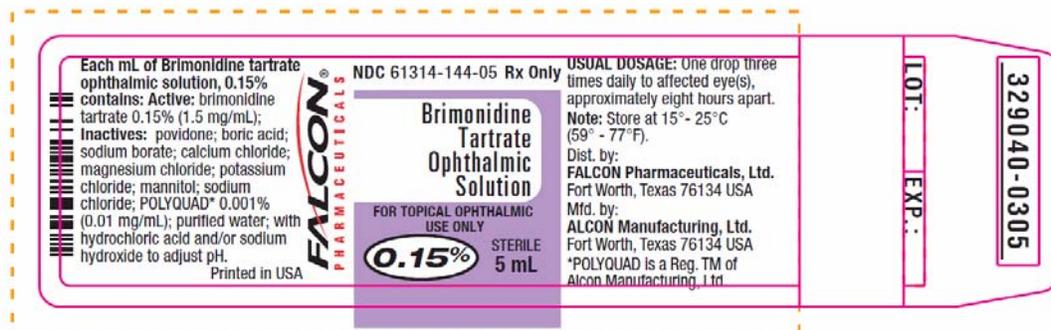
15 mL



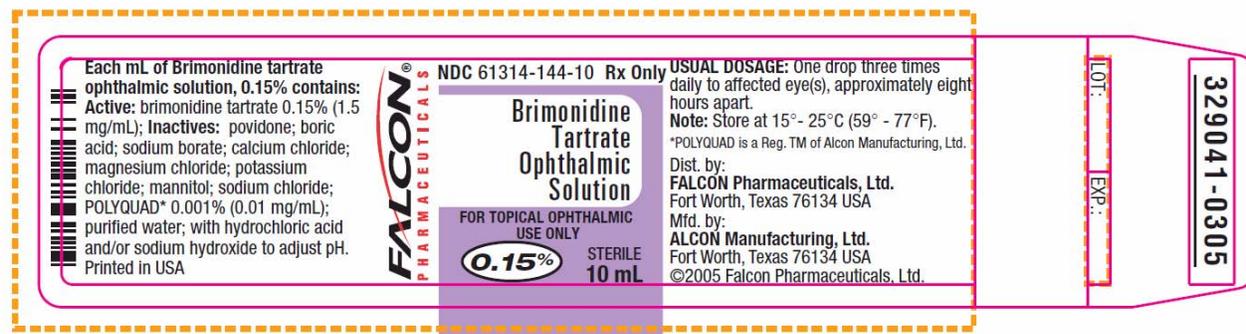
NDA 21-764
Page 10

CONTAINER LABEL

5 mL



10 mL



15 mL

