PRODUCT MONOGRAPH

BRIMONIDINE P

Brimonidine Tartrate
Ophthalmic Solution, 0.15%, w/v
Sterile

Relatively selective α_2-adrenoceptor Agonist

Elevated Intraocular Pressure Therapy

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form/Strength	Clinically Relevant Nonmedicinal Ingredients
Ophthalmic	Solution, 0.15% w/v brimonidine tartrate	Sodium Chlorite 25% w/v Solution Stabilized (as preservative), boric acid, calcium chloride dehydrate, carboxymethylcellulose sodium, magnesium chloride, potassium chloride, sodium borate, sodium chloride, water for injection and hydrochloric acid or sodium hydroxide to adjust pH.

INDICATIONS AND CLINICAL USE

BRIMONIDINE P (brimonidine tartrate) ophthalmic solution, 0.15% (preserved with sodium chlorite) is indicated for the control of intraocular pressure in patients with chronic open-angle glaucoma or ocular hypertension.

Geriatrics (> 65 years of age):
No overall difference in safety and effectiveness has been observed between elderly and other adult patients. The C_{max} and apparent half-life of brimonidine tartrate were similar in elderly subjects (65 years or older) and younger adults, indicating that its systemic absorption and elimination were not significantly affected by age.

Pediatrics (< 18 years of age):
Neonates and infants (children under the age of 2 years): The use of BRIMONIDINE P in neonates and infants is contraindicated. Several serious adverse reactions have been reported in association with the administration of brimonidine tartrate ophthalmic solution 0.2% to infants in the age range of 28 days to 3 months. **(See CONTRAINDICATIONS and ADVERSE REACTION sections).**

Children (2-18 years of age): The use of BRIMONIDINE P is currently **not recommended** in children, as several serious adverse reactions have been reported in association with the administration of brimonidine tartrate ophthalmic solution 0.2% in pediatric population. **(See**

ADVERSE REACTION, Serious Reports of Adverse Reactions in Pediatric Patients section).

CONTRAINDICATIONS

BRIMONIDINE P (brimonidine tartrate) ophthalmic solution, 0.15% is contraindicated in

- patients with hypersensitivity to brimonidine tartrate or any component of this medication. For a complete listing of nonmedicinal ingredients see the DOSAGE FORMS, COMPOSITION AND PACKAGING section of the Product Monograph
- patients receiving monoamine oxidase (MAO) inhibitor therapy
- neonates and infants (children under the age of 2 years)

WARNINGS AND PRECAUTIONS

General

FOR TOPICAL OPHTHALMIC USE ONLY.

Carcinogenesis and Mutagenesis

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 base/kg/day and 1.0 mg base/kg/day of brimonidine tartrate, respectively. These doses achieved 106 and 145 times, respectively, the plasma drug concentration estimated in humans treated with one drop of brimonidine tartrate ophthalmic solution 0.15% (with Purite™[1]) into both eyes three times per day.

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

Cardiac disorders

Although brimonidine tartrate ophthalmic solution 0.15% (with Purite™) had minimal effect on blood pressure and heart rate of patients in clinical studies, caution should be exercised in treating patients receiving brimonidine tartrate ophthalmic solution 0.15% (with Purite™) with severe cardiovascular disease.

Brimonidine tartrate ophthalmic solution 0.15% (with Purite™) should be used with caution in patients with cerebral or coronary insufficiency, Raynaud's phenomenon, orthostatic hypotension or thromboangiitis obliterans.

Hepatic/Biliary/Pancreatic

[1] Purite™ (oxychloro complex) solution is comprised of predominantly sodium chlorite.

Brimonidine tartrate ophthalmic solution 0.15% (with Purite™) has not been studied in patients with hepatic or renal impairment; caution should be exercised in treating such patients.

Ophthalmologic
Contact lenses should be removed prior to instillation of BRIMONIDINE P Ophthalmic Solution, 0.15% and may be reinserted 15 minutes after its instillation.

Psychiatric
Brimonidine tartrate ophthalmic solution 0.15% (with Purite™) should be used with caution in patients with depression.

Sensitivity/Resistance
Brimonidine tartrate ophthalmic solution 0.15% (with Purite™) should be used with caution in patients with known hypersensitivity to other alpha-adrenoceptor agonists.

Special Populations
Pregnant Women: Teratogenicity studies showed no adverse effects in rats and rabbits when oral doses (1.65 mg base/kg/day and 3.33 mg base/kg/day of brimonidine tartrate) were administered during gestation days 6 through 15 in rats and days 6 through 18 in rabbits. These doses achieved AUC values 258- and 17-fold higher, respectively, than similar values estimated in humans treated with brimonidine tartrate ophthalmic solution 0.15% (with Purite™) given as one drop in both eyes three times per day.

There are no studies of brimonidine tartrate ophthalmic solution 0.15% (with Purite™) in pregnant women, however in animal studies, brimonidine crossed the placenta and entered into the fetal circulation to a limited extent (ratio of drug-related material in fetal:maternal blood=0.1 - 0.3). Drug-derived material was eliminated from fetal tissues by 24 hours post-dose. Brimonidine tartrate ophthalmic solution 0.15% (with Purite™) should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus.

Nursing Women: Studies in rats have indicated brimonidine is excreted in the milk of the lactating rat. Since it is not known whether this drug is excreted in human 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.

Pediatrics (< 18 years of age)
Neonates and infants (children under the age of 2 years): The use of brimonidine tartrate ophthalmic solution 0.15% (with Purite™) in neonates and infants is contraindicated. Several serious adverse reactions have been reported in association with the administration of brimonidine tartrate ophthalmic solution 0.2% to infants in the age range of 28 days to 3 months. (See **CONTRAINDICATIONS** and **ADVERSE REACTIONS** sections).

Children (2-18 years of age): The use of brimonidine tartrate ophthalmic solution 0.15% (with Purite™) is currently **not recommended** in children, as **s**everal serious adverse reactions have been reported in association with the administration of brimonidine tartrate ophthalmic solution

0.2% in pediatric population. (See **ADVERSE REACTIONS, Serious Reports of Adverse Reactions in Pediatric Patients** section).

Occupational Hazards
BRIMONIDINE P (brimonidine tartrate) ophthalmic solution 0.15%, as with other similar medications, can potentially 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.

BRIMONIDINE P (brimonidine tartrate) ophthalmic solution 0.15% may also cause blurred vision or visual disturbance in some patients. The patient should wait until these symptoms have cleared before driving or using machinery.

ADVERSE REACTIONS

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

In clinical studies the most frequently reported adverse reactions (>1%) classified as treatment-related from the 12 month Phase III controlled clinical studies for patients (n=380) who received brimonidine tartrate ophthalmic solution 0.15% (with Purite™) are listed below in Table 1. Adverse events were coded using the COSTART dictionary available at the time of the study, but are presented in Table 1 below using MedDRA System Organ Class.

Table 1: Treatment Related Adverse Reactions Occurring **at ≥1% with** brimonidine tartrate ophthalmic solution 0.15% (with Purite™).

System Organ Class Preferred Term[a]	**Brimonidine-Purite™ 0.15% (n=380)**	**Brimonidine-Purite™ 0.2% (n=383)**	**Brimonidine Tartrate Ophthalmic Solution (with benzalkonium chloride) 0.2% (n=383)**
Eye disorders			
Conjunctival hyperemia	69 (18.2%)	81 (21.1%)	98 (25.6%)
Allergic conjunctivitis	35 (9.2%)	56 (14.6%)	60 (15.7%)
Eye pruritus	31 (8.2%)	42 (11.0%)	45 (11.7%)
Visual disturbance	23 (6.1%)	28 (7.3%)	30 (7.8%)
Conjunctival folliculosis	21 (5.5%)	28 (7.3%)	31 (8.1%)
Burning sensation in the eye	20 (5.3%)	28 (7.3%)	32 (8.4%)

System Organ Class Preferred Term[a]	Brimonidine-Purite™ 0.15% (n=380)	Brimonidine-Purite™ 0.2% (n=383)	Brimonidine Tartrate Ophthalmic Solution (with benzalkonium chloride) 0.2% (n=383)
Eye dryness	11 (2.9%)	19 (5.0%)	17 (4.4%)
Foreign body sensation	11 (2.9%)	13 (3.4%)	20 (5.2%)
Epiphora	10 (2.6%)	13 (3.4%)	18 (4.7%)
Eyelid edema	8 (2.1%)	13 (3.4%)	9 (2.3%)
Eye pain	7 (1.8%)	11 (2.9%)	10 (2.6%)
Blepharitis	6 (1.6%)	1 (0.3%)	6 (1.6%)
Erythema eyelid	6 (1.6%)	9 (2.3%)	9 (2.3%)
Irritation eye	6 (1.6%)	5 (1.3 %)	12 (3.1%)
Ocular stinging sensation	6 (1.6%)	1 (0.3%)	6 (1.6%)
Photophobia	6 (1.6%)	0 (0.0%)	4 (1.0%)
Conjunctival edema	5 (1.3%)	5 (1.3%)	6 (1.6%)
Eye discharge	5 (1.3%)	7 (1.8%)	15 (3.9%)
Follicular conjunctivitis	5 (1.3%)	3 (0.8%)	3 (0.8%)
Superficial punctate keratitis	5 (1.3%)	2 (0.5%)	3 (0.8%)
Visual acuity worsened	4 (1.1%)	3 (0.8%)	4 (1.0%)
Gastrointestinal disorders			
Oral dryness	20 (5.3%)	36 (9.4%)	40 (10.4%)
General disorders and administration site conditions			
Asthenia	6 (1.6%)	8 (2.1%)	16 (4.2%)
Nervous system disorder			
Headache	9 (2.4%)	7 (1.8%)	7 (1.8%)
Respiratory, thoracic and mediastinal disorders			
Rhinitis	4 (1.1%)	2 (0.5%)	1 (0.3%)

[a] MedDRA System Organ Class and Preferred Terms

Serious Reports of Adverse Reactions in Pediatric Patients:

In a 3-month, phase 3 study in children aged 2-7 years with glaucoma, inadequately controlled by beta-blockers, a high prevalence of somnolence (55%) was reported with brimonidine tartrate ophthalmic solution 0.2% as adjunctive treatment. In 8% of children, this was severe and led to discontinuation of treatment in 13%. The incidence of somnolence decreased with increasing age, being least in the 7-year-old age group (25%), but was more affected by weight, occurring more frequently in those children weighing ≤20 kg (63%) compared to those weighing >20 kg (25%).

The safety and effectiveness of brimonidine tartrate ophthalmic solution 0.15% (with Purite™) has not been studied in children under the age of two years. During post-marketing surveillance somnolence, lethargy, hypotonia, hypothermia, bradycardia, hypotension, apnoea, respiratory depression, pallor and coma have been reported in neonates, infants and children receiving brimonidine either for congenital glaucoma or via accidental ingestion.

Post-Market Adverse Drug Reactions

The following adverse reactions have been identified during postmarketing use of brimonidine tartrate ophthalmic solution 0.15% (with Purite™) in clinical practice. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made.

Eye disorders: vision blurred, conjunctivitis
General disorders and administration site conditions: fatigue, dizziness
Immune system disorders: hypersensitivity

Nervous system disorders: somnolence

The following adverse reactions have been identified during postmarketing use of brimonidine tartrate ophthalmic solution 0.2% in clinical practice. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made.

Cardiac disorders: palpitations/arrhythmias (including bradycardia or tachycardia)
Eye disorders: iritis, iridocyclitis (anterior uveitis), miosis, conjunctivitis, eyelids pruritus
Immune system disorders: hypersensitivity, skin reaction
Nervous system disorders: syncope
Psychiatric disorders: depression
Vascular disorders: hypotension

DRUG INTERACTIONS

Overview
Brimonidine tartrate ophthalmic solution 0.15% (with Purite™) did not have clinically significant effects on pulse and blood pressure in chronic clinical studies. However, since alpha-agonists, as a class, may reduce pulse and blood pressure, caution in the concomitant use of drugs such as beta-blockers (ophthalmic and/or systemic), antihypertensives and/or cardiac glycosides is advised.

Drug-Drug Interactions
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% (with Purite™) can lead to an interference in intraocular pressure (IOP) lowering effect. No data are available on the level of circulating catecholamines after brimonidine tartrate ophthalmic solution 0.15% (with Purite™) is instilled. Caution, however, is advised in patients taking tricyclic antidepressants which can affect the metabolism and uptake of circulating amines.
Although specific drug interaction studies have not been conducted with brimonidine tartrate ophthalmic solution 0.15% (with Purite™), the possibility of an additive or potentiating effect with CNS depressants (alcohol, barbiturates, opiates, sedatives, or anesthetics) should be considered.

Drug-Food Interactions
Interactions with food have not been established.

Drug-Herb Interactions
Interactions with herbal products have not been established.

Drug-Laboratory Interactions
Interactions with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

Recommended Dose and Dosage Adjustment
The recommended dose is one drop of BRIMONIDINE P (brimonidine tartrate) Ophthalmic Solution, 0.15% in the affected eye(s) three times daily, approximately 8 hours apart.

Missed Dose
NOTE: If you forget to apply your eye drops at your normal time, simply apply them as soon as you remember. Then go back to the original schedule as directed by your doctor. **Don't try to catch up on missed drops by applying more than one dose at a time.**

Administration
Do not allow the dropper tip of the bottle to touch the eye or other surrounding structures, because this could cause eye injury or contaminate the tip with common bacteria known to cause eye infections. Serious damage to the eye with subsequent loss of vision may result if you use eye drop solutions that have become contaminated. If you experience any type of eye condition or have surgery, immediately seek your doctor's advice concerning the continued use of the bottle you are using.

Patients Wearing Soft Contact Lenses:
Lenses should be removed prior to application of BRIMONIDINE P (brimonidine tartrate) Ophthalmic Solution, 0.15% and not re-inserted earlier than 15 minutes after use.

OVERDOSAGE

In ophthalmic overdose cases that have been 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. Evacuation of the stomach should be considered during the first few hours after an overdosage.

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 brimonidine tartrate ophthalmic solution 0.15% (preserved with Purite™) as part of medical treatment of congenital glaucoma or by accidental oral ingestion (please refer to CONTRAINDICATIONS).

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Brimonidine tartrate is a relatively selective alpha-2 adrenergic receptor agonist that, in radioligand binding assays and in functional assays, is approximately 1000 times more selective for the alpha-2 adrenoceptor than the alpha-1 adrenoceptor. This selectivity results in the absence of vasoconstriction in microvessels associated with human retinal xenografts.

Topical administration of brimonidine decreases IOP in humans. When used as directed, brimonidine tartrate ophthalmic solutions reduce elevated IOP with minimal effect on cardiovascular parameters.

Brimonidine tartrate has a rapid onset of action, with the peak ocular hypotensive effect occurring at approximately two hours post-dosing. The duration of effect is 12 hours or greater.

Fluorophotometric studies in animals and humans suggest that brimonidine tartrate has a dual mechanism of action. Brimonidine tartrate ophthalmic solution 0.15% (preserved with Purite™) lowers IOP by reducing aqueous humor production and increasing uveoscleral outflow.

Pharmacodynamics
Brimonidine tartrate ophthalmic solution 0.15% (with Purite™) has no effect on pulmonary function or exercise-induced tachycardia. The cardiovascular effects of brimonidine tartrate ophthalmic solution 0.15% (with Purite™) during exercise in normal volunteers were found to be limited to a slight suppression of systolic blood pressure, which was clinically insignificant, during the recovery period following a treadmill test.

Pharmacokinetics
After ocular administration of Brimonidine-Purite™ ophthalmic solution 0.1% or 0.2% (brimonidine tartrate 0.1% or 0.2% preserved with Purite™), plasma concentrations peaked within 0.5 to 2.5 hours, and declined with a systemic half-life of approximately 2 hours.

In humans, brimonidine is eliminated rapidly via extensive systemic metabolism; there is no marked systemic accumulation after multiple dosing. 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.

STORAGE AND STABILITY

BRIMONIDINE P Ophthalmic Solution, 0.15% should be stored at room temperature between 15°C to 30°C (59°F - 86°F). Discard unused solution at the end of treatment.

SPECIAL HANDLING INSTRUCTIONS

Patients should be advised to keep the dropper tip of the bottle from touching the eye or other surrounding structures, because of the potential for eye injury and bacterial contamination. Serious damage to the eye with subsequent loss of vision may result if you use eye drop

solutions that have become contaminated. If you experience any type of eye condition or have surgery, immediately seek your doctor's advice concerning the continued use of the bottle you are using.

DOSAGE FORMS, COMPOSITION AND PACKAGING

BRIMONIDINE P (brimonidine tartrate) Ophthalmic Solution, 0.15% is supplied in white, opaque plastic dropper bottles with a white cap and sealing tape, containing 5 mL, 10 mL or 15 mL.

Each mL of BRIMONIDINE P Ophthalmic Solution, 0.15% contains brimonidine tartrate 1.5 mg with the following non-medicinal ingredients: Sodium Chlorite 25% w/v Solution Stabilized (as preservative), boric acid, calcium chloride dihydrate, carboxymethylcellulose sodium, magnesium chloride, potassium chloride, sodium borate, sodium chloride, water for injection and hydrochloric acid or sodium hydroxide to adjust the pH.

PART II: SCIENTIFIC INFORMATION

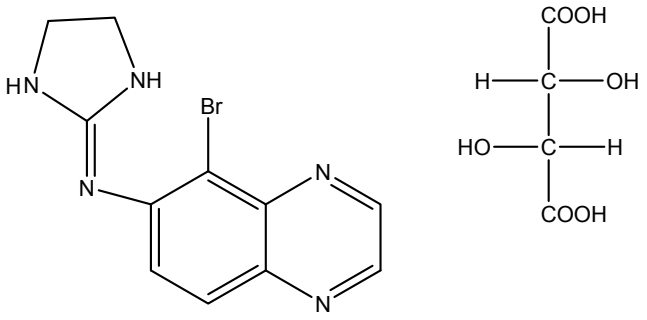
PHARMACEUTICAL INFORMATION

Drug Substance

Common name: Brimonidine tartrate

Chemical name: 5-Bromo-6-(2-imidazolidinylideneamino) quinoxaline L-tartrate

Structural formula:



Molecular formula: $C_{11}H_{10}BrN_5$ $C_4H_6O_6$

Molecular weight: 442.2

Description: Brimonidine tartrate is an off-white, pale yellow to pale pink powder, with a melting point range of 202 - 210°C. It is water soluble (34 mg/mL) and soluble in DMSO (>60 mg/mL), slightly soluble in propylene glycol (~1.0 mg/mL), and very slightly soluble in ethanol (0.6 mg/mL) and acetone (<0.2 mg/mL). The pH of a 1% solution of brimonidine tartrate in water is 3.5 at room temperature. A pK_a value of 7.78 ± 0.05 has been determined.

CLINICAL TRIALS

Study demographics and trial design

Table 2: Trials conducted in patients with open-angle glaucoma or ocular hypertension

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)		Mean age (Range)	Gender (M/F)
			No. Entered	No. Completed		
190342-007	Multicenter, double-masked, randomized, active-controlled, parallel study in patients with OAG or OHT	One drop (~35 µL) in each eye three times daily 12 months	593	398 Brimonidine-Purite™ 0.15% = 131 Brimonidine-Purite™ 0.2% = 135 Brimonidine Tartrate Ophthalmic Solution (with benzalkonium chloride) (0.2%) = 132	61.4 (25-93)	43.8%/56.2%
190342-008	Multicenter, double-masked, randomized, active-controlled, parallel study in patients with OAG or OHT	One drop (~35 µL) in each eye three times daily 12 months	554	344 Brimonidine-Purite™ 0.15% = 117 Brimonidine-Purite™ 0.2% = 110 Brimonidine Tartrate Ophthalmic Solution (with benzalkonium chloride) (0.2%) = 117	65.3 (22-90)	43.0%/57.0%

Note: OAG= open-angle glaucoma, OHT=ocular hypertension

Study results

Brimonidine tartrate lowers intraocular pressure with minimal effect on cardiovascular parameters (heart rate, systolic and diastolic blood pressure) and no apparent effect on pulmonary parameters (spirometry, respiratory rate).

Two clinical studies (n=1,147) lasting for twelve months were conducted to evaluate the safety, efficacy, and acceptability of brimonidine tartrate ophthalmic solution 0.15% (with Purite™) and 0.2% Brimonidine-Purite™ compared with brimonidine tartrate ophthalmic solution 0.2% (preserved with benzalkonium chloride), administered three-times-daily in patients with glaucoma or ocular hypertension. The intraocular pressure values for the Baseline and Month-12 time points using brimonidine tartrate ophthalmic solution 0.15% (with Purite™) and 0.2% (with benzalkonium chloride) are summarized in Table 3 below.

Table 3: Intraocular Pressure Val ues (mm Hg) Phase 3 Studies (ITT LOCF ANALYSIS)

		Study 190342-007		Study 190342-008	
		Brimonidine Tartrate Ophthalmic Solution (with Purite™) (0.15%) N=197	**Brimonidine Tartrate Ophthalmic Solution (with benzalkonium chloride) (0.2%) N=199**	**Brimonidine Tartrate Ophthalmic Solution (with Purite™) (0.15%) N=184**	**Brimonidine Tartrate Ophthalmic Solution (with benzalkonium chloride) (0.2%) N=184**
Baseline	**Hour-0** Mean	24.9	24.7	24.9	25.3
	Hour-2 Mean	23.1	23.0	23.6	24.1
	Hour-7 Mean	21.8	21.9	22.4	23.0
	Hour-9 Mean	21.7	21.6	22.4	23.1
Month-12	**Hour-0** Mean (mean change from baseline)	21.6 (-3.3)	21.3 (-3.4)	22.3 (-2.6)	22.7 (-2.6)
	CI[a]	(-0.61, 1.01)		(-1.44, 0.45)	
	Hour-2 Mean (mean change from baseline)	18.6 (-4.5)	18.1 (-4.9)	19.3 (-4.3)	19.3 (-4.8)
	CI[a]	(-0.35, 1.16)		(-0.62, 1.09)	
	Hour-7 Mean (mean change from baseline)	19.9 (-1.9)	19.6 (-2.3)	20.4 (-2.0)	21.0 (-2.0)
	CI[a]	(-0.59, 0.92)		(-1.09, 0.58)	
	Hour-9 Mean (mean change from baseline)	17.9 (-3.8)	17.4 (-4.2)	18.5 (-3.9)	18.5 (-4.6)
	CI[a]	(-0.27, 1.18)		(-0.41, 1.29)	

a = 95% confidence interval for difference between brimonidine tartrate ophthalmic solution 0.15% (with Purite™) and 0.2% (with benzalkonium chloride) concentrations

NOTE:

N = number of patients at baseline, CI = confidence interval

There was no statistical significance between brimonidine tartrate ophthalmic solution 0.15% (with Purite™) and 0.2% (with benzalkonium chloride) for within group analysis of changes from baseline using a paired t-test (at all time points the p-value was <0.001)

Efficacy analyses from these two clinical trials indicated that brimonidine tartrate ophthalmic solution 0.15% (with Purite™) is non-inferior to brimonidine tartrate ophthalmic solution 0.2% (with benzalkonium chloride) and effectively lowered IOP in patients with glaucoma or ocular hypertension (mean values of at least 2.6 mm Hg at trough, and at least 4.3 mm Hg at peak) over the twelve months of the study. Brimonidine tartrate ophthalmic solution 0.15% (with Purite™) was well tolerated, rated as comfortable by the majority of patients, and provided a superior safety profile when compared with brimonidine tartrate ophthalmic solution 0.2% (with benzalkonium chloride). Among the most commonly reported adverse events (≥3.9% incidence in the brimonidine tartrate ophthalmic solution 0.15% [with Purite™] group), the frequency of reports were generally fewer than with brimonidine tartrate ophthalmic solution 0.2% (with benzalkonium chloride). There was a significantly smaller percentage of patients who experienced allergic conjunctivitis, oral dryness, asthenia, or somnolence in the brimonidine tartrate ophthalmic solution 0.15% (with Purite™) group. Brimonidine tartrate ophthalmic

solution 0.15% (with Purite™) was the lowest effective dose of brimonidine tartrate efficacy with the most favorable safety and tolerability profile.

DETAILED PHARMACOLOGY

Animal Pharmacology

Receptor binding and functional studies have characterized brimonidine as a potent and selective alpha-2-adrenoceptor agonist. As indicated in Table 4, brimonidine is notably more alpha-2 adrenoceptor selective than clonidine and *p*-aminoclonidine in both radioligand binding and functional assays.

Table 4: Receptor Pharmacology of Brimonidine, Clonidine and *p*-Aminoclonidine

Radioligland Binding; Ki (nM)*			Functional; EC_{50} (nM)*	
Compound	**Alpha-1[a]**	**Alpha-2[b]**	**Alpha-1[c]**	**Alpha-2[d]**
Brimonidine	1850 ± 322 (5)	1.9 ± 0.5 (6)	1490 ± 214 (12)	1.0 ± 0.1 (24)
Clonidine	513 ± 108 (4)	3.4 ± 0.4 (6)	293 ± 47 (4)	4.4 ± 0.4 (11)
p-Aminoclonidine	181 ± 18 (4)	7.8 ± 1.2 (2)	180 ± 10 (8)	1.9 ± 0.2 (9)

*Mean ± SEM; 'N' is noted in parentheses.
[a][^{3}H]Prazosin in human cerebral cortex.
[b][^{3}H]Rauwolscine binding in HT-29 cells.
[C]Contraction of isolated rabbit aorta.
[d]Inhibition of electrically induced contractions in the isolated rabbit vas deferens.

The ocular hypotensive effect of brimonidine has been demonstrated in normotensive rabbits, cats, and monkeys, as well as ocular hypertensive rabbits and monkeys. This effect is maintained following six months of chronic administration to albino rabbits (Table 5).

Table 5: The IOP Response to Chronic Administration of Brimonidine (BID for 6 months) in Rabbits

Concentration (%)[a]	Acute	Three Months	Six Months
0.08	4.3[b]*	5.1*	3.8*
0.2	4.0*	6.0*	5.1*
0.5	0.2	6.0*	6.9*
0.8	1.0	6.5*	7.1*

[a] Concentration based on the bitartrate salt.
[b] Mean decrease in treated eye IOP (mm Hg) from vehicle-treated control at 2 hr following the AM dose.
* Significantly different from vehicle-treated animals ($p<0.05$) for treated eye.

Twenty-eight days of BID dosing of brimonidine tartrate 0.5% to rabbits and monkeys demonstrated that monkeys experience a significantly diminished trough ocular hypotensive effect on chronic dosing. In rabbits, the trough IOP effect was unaltered, however, the peak effect significantly increased with this dosing regimen (confirmed also by 6 month experiments - see Table 5).

The mechanism of action for the ocular hypotensive effect of brimonidine in rabbits and monkeys is predominantly the suppression of aqueous humor production. Trabecular outflow

was not found to be affected in monkeys. In rabbits, a secondary mechanism of action includes an enhancement of uveoscleral outflow.

Investigational studies have demonstrated that topically administered brimonidine stimulates a peripheral alpha-2 adrenoceptor to lower IOP in rabbits. SKF 104078, the selective postjunctional alpha-2 receptor antagonist, did not block the ocular hypotensive effects of brimonidine in rabbits, suggesting that the vascular postjunctional alpha-2 adrenoceptor is not involved in the IOP response in this species. The data in monkeys suggest that the IOP and cardiovascular responses to brimonidine are mediated by an imidazoline receptor located in the central nervous system (CNS). The miotic response to brimonidine which occurs in monkeys is mediated by an alpha-2 adrenoceptor.
When the action of brimonidine as a neuroprotective agent was evaluated in *in vitro* and *in vivo* pharmacological studies in rat, no deleterious effects on the optic nerve were observed.

Human Pharmacology
Mechanism of Action: The effect of brimonidine on aqueous humour dynamics was determined in 21 ocular hypertensive patients. Measurements were made at baseline and following one week (Day 8) of twice daily application of one drop of brimonidine tartrate 0.2% to one eye and vehicle to the fellow eye, in a double-blind fashion.

The results of this study (mean±SEM) are reported in Table 6. They indicate that brimonidine reduces IOP in humans by decreasing aqueous inflow and increasing uveoscleral outflow.

Table 6: Effects of Brimonidine on Aqueous Humour Dynamics

	Control Eye		**Treated Eye**	
	Baseline	**Day 8**	**Baseline**	**Day 8**
lOP	21.3 ± 1.0	20.0 ± 0.6*	20.6 ± 0.8	15.9 ± 0.6*†
Fa	2.6 ± 0.2	2.3 ± 0.1*	2.5 ± 0.2	2.0 ± 0.1 *
Fu_{fl}	0.35 ± 0.20	0.50 ± 0.17	0.12 ± 0.28	0.65 ± 0.16*
Fu_{ton}	0.28 ± 0.31	0.08 ± 0.35	0.25 ± 0.37	1.02 ± 0.11*†
C_{fl}	0.22 ± 0.03	0.16 ± 0.02*	0.22 ± 0.03	0.21 ± 0.03
C_{ton}	0.17 ± 0.01	0.19 ± 0.02	0.19 ± 0.03	0.16 ± 0.02
Pev	8.9 ± 0.5	8.5 ± 04	8.8 ± 0.5	9.2 ± 0.3

*p≤0.05 vs baseline; †p≤0.05 vs control

Pharmacodynamics: In short-term studies (up to four days) in normal healthy volunteers, brimonidine tartrate ophthalmic solutions preserved with benzalkonium chloride lowered IOP (intraocular pressure) significantly better than vehicle at all concentrations tested (0.02-0.5%) and was found to be safe and comfortable. At these concentrations, the peak effect on IOP was observed between one and four hours post-instillation. The greatest reduction in IOP was dose-related, reaching a maximal decrease from baseline of up to 40% with brimonidine tartrate 0.5%. In the morning (12 hours after the evening instillation), the 0.08% and 0.2% concentrations reached a maximal IOP lowering effect following two days of BID dosing. This was observed with the 0.5% concentration, however, 12 hours after the first instillation. Conjunctival blanching was observed primarily at the 0.35% and 0.5% concentrations, and was generally mild or moderate in nature. There was a significantly greater incidence of dry eye seen only with

brimonidine tartrate 0.5% as compared to vehicle, although this finding was also reported at the lower concentrations. The overall mean decrease in pupil size and systolic blood pressure was generally greater with brimonidine 0.2% and 0.5% than with vehicle. This change in systolic blood pressure was not judged to be clinically significant. Heart rate, diastolic blood pressure, visual acuity and cup-disc ratio did not appear to be significantly affected by brimonidine treatment (as compared to vehicle). Additionally, at the concentrations tested in these healthy volunteer studies, a contralateral effect of brimonidine was not observed.

When evaluated in open-angle glaucoma and ocular hypertensive patients at concentrations of 0.08%, 0.2% and 0.5% for one month (BID), brimonidine tartrate *was* found to be both efficacious and safe. All concentrations tested were significantly more effective than vehicle in lowering elevated IOP. The two higher concentrations of brimonidine tartrate were also more effective than the 0.08% concentration. Brimonidine tartrate 0.5%, however, was not any more effective than 0.2% for long-term treatment. The peak effect on IOP occurred at two hours for brimonidine tartrate 0.08%, 0.2%, and 0.5%. The greatest decrease in IOP was dose-related, with a maximum reduction of 27% from baseline with brimonidine tartrate 0.2%, and 31% from baseline with brimonidine tartrate 0.5%. Brimonidine tartrate 0.5% was associated with a greater incidence of side effects than brimonidine tartrate 0.2% and 0.08%, including blurring, foreign body sensation, fatigue and drowsiness. Dry mouth was seen more often in all active treatment groups than in the vehicle group. This event was also seen at a higher incidence with brimonidine tartrate 0.5% than with brimonidine tartrate 0.08%. Although heart rate did not appear to be significantly affected by brimonidine treatment, diurnal measurements of blood pressure indicated that brimonidine tartrate 0.5% was associated with a greater decrease than was vehicle or the lower brimonidine strengths. The mean blood pressure decreases observed were not considered to be clinically significant.

Two 1-month, dose-response studies (n=222) were conducted to evaluate the efficacy and safety of Brimonidine-Purite™, dosed either twice-daily or three-times-daily, compared with brimonidine tartrate ophthalmic solution 0.2% (with benzalkonium chloride), Timoptic®, and vehicle. Brimonidine-Purite™ 0.1% and 0.2% lowered IOP significantly, compared to vehicle when dosed twice or three times daily. However, Brimonidine-Purite™ 0.1% was less effective than Brimonidine-Purite™ 0.2%, brimonidine tartrate ophthalmic solution 0.2% (with benzalkonium chloride), or Timoptic®, regardless of its dosing regimen. Both Brimonidine-Purite™ 0.1% and 0.2% demonstrated acceptable safety profiles.

Systemic Pharmacokinetics

Systemic absorption of brimonidine after ocular administration of a single dose (both eyes) of brimonidine tartrate 0.08%, 0.2% and 0.5% to healthy volunteers, produced dose-dependent increases in C_{max} and AUC. AUC increased proportionally with dose between the 0.08% and 0.2% doses; the increase in AUC of the 0.5% dose was less than proportional with the increase in dose. Following the 0.5% dose, plasma C_{max} and $AUC_{0-\infty}$ were approximately 0.1 ng/mL and 0.5 ng·hr/mL, respectively. The mean T_{max} was 2-3 hours for all concentrations tested in this study. In general, plasma concentrations declined to undetectable levels by 12 hours post-dose. The apparent plasma $t_{1/2}$ ranged from 2 to 5 hours (mean=3.3 hours).

Plasma concentration-time profiles were similar for both young and elderly healthy volunteers following ocular instillation of a single dose of brimonidine tartrate 0.2%, although the elderly subjects showed a tendency to have a slightly greater systemic exposure to brimonidine. Steady state concentrations were reached by day 7 of multiple dosing (both eyes, BID) in young (23-39 years) subjects. Twice daily ocular dosing for 10 days did not change the systemic absorption and disposition parameters of brimonidine in young subjects. The mean C_{max} was 0.0585 ng/mL and mean AUC_{0-12} was 0.309 ng·hr/mL after multiple dosing. There was a slight systemic drug accumulation after repeated dosing (accumulation factor: 1.4), consistent with an apparent half-life of 3 hours. Beyond 12 hours after the final dose, plasma concentrations were undetectable or approached the limit of quantitation. Systolic and diastolic blood pressures were generally lowered by brimonidine tartrate administration. These decreases in blood pressure tended to be slightly greater among the elderly subjects than among the young subjects.

Plasma brimonidine concentrations and serum glucose concentrations during brimonidine tartrate treatment TID were investigated in a single-center, randomized, double-masked, vehicle-controlled, parallel study of 0.1% and 0.2% brimonidine tartrate ophthalmic solution preserved with Purite™ in healthy subjects. Concentration-time profiles of brimonidine were assessed on days 1 and 7.

Plasma brimonidine concentrations were proportional to dose, and during treatment with 0.2% brimonidine tartrate ophthalmic solution preserved with Purite™, were comparable to those measured during treatment with brimonidine tartrate ophthalmic solution preserved with benzalkonium chloride (brimonidine tartrate ophthalmic solution 0.2%). Plasma C_{max} during TID treatment with brimonidine tartrate ophthalmic solution 0.15% (preserved with Purite™) are expected to be approximately 47.4 pg/mL, compared to 58.5 pg/mL during BID treatment with brimonidine tartrate ophthalmic solution 0.2% (with benzalkonium chloride). Systemic accumulation was minimal. Brimonidine did not affect systemic glucose disposition or serum glucose levels.

TOXICOLOGY

Acute Toxicity

The acute median lethal dose (LD_{50}) or minimum lethal dose (MLD) values of brimonidine were evaluated in mice, rats, rabbits, and dogs by oral and intravenous (i.v.) administration. The LD_{50} or MLD values for each study are listed below:

Species	Route	LD_{50} (mg/kg)*	MLD (mg/kg)*
Mouse	oral	50	>8**
	i.v*	50	Not performed
Rat	oral	100	>8**
	i.v.	100-150	Not performed
Rabbit	oral	Not performed	>6
	i.v.	Not performed	20-50
Dog	oral	Not performed	0.5
	i.v.	Not performed	0.05

* The doses are expressed as the base except in the mouse and rat MLD data, where they are expressed as brimonidine tartrate.
**The data from additional single dose oral studies of 0.2% and 0.5% solutions of brimonidine tartrate in mice and rats showed that the oral MLD is greater than 10 mg/kg.

The most frequently observed clinical signs in the acute/single dose toxicity studies were primarily due to the exaggerated pharmacological hypotensive effect of the compound. These signs included: sedation, ataxia, prostration, ptosis, reduced/loss of blink reflex, opacification of the cornea, hypotension, bradycardia, hypothermia, respiratory depression, respiratory arrest and circulatory collapse. The ocular changes were seen only after doses at or above the minimum lethal dose.

Long-term Toxicity

Long-term toxicity studies with brimonidine tartrate in various concentrations using mice, rats, rabbits, dogs and monkeys were conducted for durations of up to one year. The most notable effects seen in these studies were related to the known pharmacological effect of brimonidine.

Brimonidine was administered in repeated oral doses to mice (3 studies -12 to 13 weeks), rats (6 studies - 6 days to 1 year), dogs (2 studies - 4 to 14 weeks) and monkeys (2 studies - 1 year each). It was also administered occularly to rabbits (2 studies - 1 and 6 months) and dogs (1 study - 4 weeks) and monkeys (1 study - 1 year). There were no observable adverse effects in oral dosing of mice at approximately 145 times the recommended ocular human dose, rats at approximately 70 times the recommended ocular human dose, rabbits at approximately 22 times the recommended ocular human dose, dogs at approximately 50 times the recommended ocular human dose, and monkeys at approximately 30 times the recommended ocular human dose. Dosage levels of approximately 295 times greater than those recommended for human ocular use showed toxic effects that were consistent with the pharmacological class of the compound.

Chronic oral dosing studies were performed at extreme levels of approximately 2650 times the recommended human ocular dose. At these extreme doses, mice showed goblet cell hyperplasia and depletion in the rectum and colon, hypertrophy of the tunica muscularis of small and large intestine, and hyperplasia of the non-glandular epithelium of the stomach. Rats dosed orally at approximately 1330 times the human ocular dose, showed thickening of muscularis mucosa of small intestine, and a dose related incidence of illeal intussusception was observed in all rats, but no associated lesions or morphological changes were observed. Evidence of toxicity characterised by decreased body weight gain and/or decreased food consumption was often seen at the higher oral doses in the mouse, rat and monkey. The most notable effects seen in the subacute studies was an exaggerated pharmacological effect characterised by sedation, ataxia, hypoactivity, ptosis, decreased muscle tone, hypotension and bradycardia.

There were no observable adverse effects in ocular dosing of rabbits up to approximately 105 times the recommended ocular human dose, dogs up to approximately 18 times the recommended ocular human dose, and monkeys up to approximately 35 times the recommended ocular human dose.

A long-term study was conducted with Brimonidine-Purite™ 0.1% or 0.2% administered to New Zealand White rabbits as 1 drop in 1 eye 3 times daily for 6 months. Both formulations were

well tolerated. Slight, short term, dose-related sedation and hyperglycemia (up to 2.2-fold) were observed. These effects were considered exaggerated pharmacologic effects of alpha-2-adrenergic receptor activation. Plasma C_{max} and AUC_{0-24} hr values were increased 20 and 6 times, respectively, the similar values estimated in humans treated with 1 drop of brimonidine tartrate ophthalmic solution 0.15% (with Purite™) in both eyes three times per day.

Carcinogenicity
No compound-related carcinogenic effects were observed in either mice or rats following a 21-month and 24-month study, respectively. 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 106 and 145 times, respectively, the plasma drug concentration estimated in humans treated with one drop brimonidine tartrate ophthalmic solution 0.15% (with Purite™) into both eyes three times per day.

Mutagenicity
Brimonidine was not mutagenic or cytogenic in a series of *in vitro* and *in vivo* studies including the Ames test, host-mediated assay, chromosomal aberration assay in Chinese Hamster Ovary (CHO) cells, cytogenic studies in mice and dominant lethal assay.

Reproduction and Teratology
No impairment of fertility and reproduction occurred in male rats when treated for 70 days prior to mating and female rats when treated for 14 days prior to mating and continuing through gestation and lactation with oral doses of brimonidine tartrate. Although blood drug levels were not determined in this study, it is estimated that the highest dose of brimonidine tartrate (0.66 mg/kg/day), achieved AUC values 60 times those seen in humans treated with 1 drop brimonidine tartrate ophthalmic solution 0.15% (with Purite™) in both eyes three times per day.

Teratogenicity studies have been performed in rats and rabbits. Brimonidine tartrate was not teratogenic when given orally during gestation days 6 through 15 in rats and days 6 through 18 in rabbits. The highest doses of brimonidine tartrate in rats (1.65 mg/kg/day) and rabbits (3.33 mg/kg/day) achieved AUC values 258 and 17-fold higher, respectively, than similar values estimated in humans treated with brimonidine tartrate ophthalmic solution 0.15% (with Purite™) 1 drop in both eyes three times per day.

After oral dosing of ^{14}C-brimonidine in pregnant rats, brimonidine crossed the placenta and entered into the fetal circulation to a limited extent, producing ^{14}C brimonidine concentrations in fetal blood that were 10-27% of that in maternal blood. Brimonidine was predominant in the placenta, uterus, and fetal liver but not in the maternal liver.

The reproductive capabilities (survival, development, and behavior), of F1 and F2 generation rats were not affected when brimonidine tartrate was administered orally to F0 generation rats from gestation, day 16, through lactation, day 20. Although blood drug levels were not determined in this study, the high dose of brimonidine tartrate (0.66 mg/kg/day) was estimated to achieve AUC values that were 60-fold higher than similar values estimated in humans treated with brimonidine tartrate ophthalmic solution 0.15% (with Purite™) 1 drop in both eyes three times per day.

There were no treatment-related reproductive and teratological effects observed in the F1 rat pup group, although a reduction in body weight was observed at a dose level of 1.65 mg base/kg/day, after 14 days. Dose related reduction in body weight gains were observed in rat dams at dose levels of 0.66 and 1.65 mg base/kg/day after 15 days.

In one rabbit study, body weight gain and food consumption in the low and mid-dose groups was comparable to the control group throughout the study. Spontaneous abortions occurred in two of eight rabbits at the 3.3 mg base/kg/day level (gestation day 21 or 23), and may have been the result of the exaggerated pharmacological effects observed at this level. No abortions occurred at the 0.165 or 0.66 mg base/kg/day level. Maternal necropsy was generally unremarkable. There was no evidence of treatment-related embryotoxicity, fetal toxicity, or teratogenicity at dosage levels up to 3.3 mg base/kg/day (approximately 980 times the recommended human ocular dose). In another study involving 20 rabbit dams, dosed orally up to 2.64 mg base/kg/day, no adverse effects were observed other than a decrease in weight gain during the dosing period, and no treatment related embryolethal or teratogenic effects were observed.

REFERENCES

1. Barnebey HS, Robin AL, Zimmerman TJ, Morrison JC, et al. The efficacy of brimonidine in decreasing elevations in intraocular pressure after laser trabeculoplasty. Ophthalmology 1993; 100: 1083-1088.

2. Burke J, Manlapaz C, Kharlamb A, Runde E, Padillo E, Spada C, Nieves A, Munk S, MacDonald T, Garst M, Rosenthal A, Batoosingh A, David R, Walt J, Wheeler L. Therapeutic use of α2-adrenoceptor agonists in glaucoma. In: Lanler S, Linbird L, eds. Alpha2-adrenergic receptors: Structure, function and therapeutic implications. Reading, United Kingdom, Harwood Academic Publishers, 1996 (in press).

3. Derik RJ, Walters TR, Robin AL, et al. Brimonidine tartrate: A one month dose response study. Invest Ophthalmol Vis Sci 1993; 34(4): 929 (1138).

4. Pasquale LR, Nordlund JR, Robin AL, Rudikoff MT, Ordman J, Walt JG, Chen KS. A comparison of the cardiovascular and pulmonary effects of brimonidine 0.2%, timolol 0.5% and betaxolol suspension 0.25%. Invest Ophthalmol Vis Sci 1993; 34(4): 929 (1139).

5. Spaeth GL, David R, Clevenger CE, Perell HF, Siegel LI. The effects of brimonidine tartrate on the incidence of intraocular pressure (IOP) spikes following argon laser trabeculoplasty. Invest Ophthalmol Vis Sci 1992; 33(4): 1159 (2340).

6. Toris CB, Camras CB, Yablonski ME. Effects of brimonidine on aqueous humour dynamics in human eyes. Invest Ophthalmol Vis Sci 1994; 35(4): 2052 (3703).

7. Walters TR, Repass RL, Sargent JP, et al. A pilot study of the efficacy and safety of AGN 190342-LF 0.02% and 0.08% in patients with elevated intraocular pressure. Invest Ophthalmol Vis Sci 1991; 32(4): 988 (1572).

8. Adverse Drug Reactions Reports filed with Allergan Inc. 1997/98.

9. Lai RK, Hasson D, Chun T, Wheeler L. Neuroprotective effect of ocular hypotensive agent brimonidine. XIth Congress of the European Society of Ophthalmology, 439-444, 1997.

10. Product Monograph. Alphagan P® (Brimonidine Tartrate) Ophthalmic Solution, 0.15%. Allergan Inc, Date of Revision: October 8, 2013, control number: 166703.

PART III: CONSUMER INFORMATION
Pr BRIMONIDINE P

Brimonidine Tartrate
Ophthalmic Solution, 0.15%, w/v
Sterile

This leaflet is part III of a three-part "Product Monograph" published when BRIMONIDINE P was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about BRIMONIDINE P. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
BRIMONIDINE P eye drops are used to control intraocular pressure in patients with chronic open-angle glaucoma or ocular hypertension.

What it does:
BRIMONIDINE P is a preserved eye drop solution that reduces the amount of fluid flowing into the eye and increases the amount of fluid flowing out of the eye. This reduces the pressure inside the eye

When it should not be used:
Do not use BRIMONIDINE P:

- If you are allergic to brimonidine tartrate or any of the other ingredients (See what the nonmedicinal ingredients are)
- If you are receiving monoamine oxidase (MAO) inhibitor therapy
- In neonates and infants below the age of 2 years

What the medicinal ingredient is:
Brimonidine Tartrate

What the important nonmedicinal ingredients are:
Sodium Chlorite 25% w/v Solution Stabilized (as preservative), boric acid, calcium chloride dihydrate, carboxymethylcellulose sodium, magnesium chloride, potassium chloride, sodium borate, sodium chloride, water for injection and hydrochloric acid or sodium hydroxide to adjust the pH.

What dosage forms it comes in:
Ophthalmic solution, brimonidine tartrate 0.15%, w/v

WARNINGS AND PRECAUTIONS

BRIMONIDINE P may cause drowsiness and fatigue or blurred vision. Do not drive, use heavy machinery or engage in hazardous activities or activities requiring mental alertness, until these conditions have passed.

BEFORE you use **BRIMONIDINE P** talk to your doctor or pharmacist if:

- you are breastfeeding a baby, pregnant or intend to become pregnant.
- you have any allergies to this drug, or to similar drugs (ask your doctor) or to **BRIMONIDINE P**'s ingredients or components of its container.
- you are taking or intend to take other prescription or non-prescription drugs. This is particularly important if you are taking medicine to lower blood pressure or to treat heart disease.
- you wear contact lenses. Lenses should be removed prior to application of **BRIMONIDINE P** and kept out for 15 minutes after use.

INTERACTIONS WITH THIS MEDICATION

Drugs that may interact with **BRIMONIDINE P** include:

Central nervous system depressants (alcohol, barbiturates, opiates, sedatives, or anesthetics), heart and blood pressure medications such as alpha-agonists, medication such as beta-blockers (ophthalmic and/or systemic), antihypertensives, cardiac glycoside, tricyclic antidepressants and clonidine.

Drug interactions studies have not been done for **BRIMONIDINE P**.

PROPER USE OF THIS MEDICATION

Usual adult dose:
Normally, you should put one drop of **BRIMONIDINE P** in each eye that needs treatment, three times daily, about 8 hours apart, following the instructions for use below.

You must not use the bottle if the tamper-proof seal on the bottle neck is broken before you first use it.

Follow the following steps to help you use **BRIMONIDINE P** properly:

1. Wash your hands. Tilt your head back and look at the ceiling.
2. Gently pull down the lower eyelid to create a small pocket.
3. Turn the bottle upside down and squeeze it gently to release one drop into each eye that needs treatment.
4. Let go of the lower lid, and close your eye for 30 seconds.

If a drop misses your eye, try again.

BRIMONIDINE P contains a preservative called PURITE™. If you wear contact lenses, remove them before using **BRIMONIDINE P**. Wait 15 minutes after using the drops before you put your lenses back in.

IMPORTANT: PLEASE READ

Always use **BRIMONIDINE P** exactly as your doctor has instructed you. If you use **BRIMONIDINE P** with another eye drop, leave at least five minutes between putting in **BRIMONIDINE P** and then the other drops.

To help prevent infections, do not let the tip of the bottle touch your eye or anything else. Put the cap back on and close the bottle immediately after you have used it.

Overdose:
If you accidentally use too many drops, just go back to your regular twice a day dosing the next day. If you have any concerns, talk to your doctor or pharmacist.

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:
If you forget to apply your eye drops at your normal time, simply apply them as soon as you remember. Then go back to the original schedule as directed by your doctor. **Don't try to catch up on missed drops by applying more than one dose at a time.**

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Very common	Occurs in more than 1 out of 10 patients
Common	Occurs in between 1 and 10 out of every 100 patients
Uncommon	Occurs in between 1 and 10 out of every 1000 patients

The following side effects may be seen with **BRIMONIDINE P.** If these persist or cause you concern, consult your doctor.

Very common:
- Red eye

Common:
- Eye allergy
- Itchy eyes
- Visual disturbance
- Small bumps on the eye surface
- Dryness of the mouth
- Burning and stinging of the eye
- Dry eyes
- A feeling that something is your eye
- Watery eyes
- Eye and eyelid swelling
- Red, itchy eyelids
- Eye pain
- Sticky eyes
- Light sensitivity
- Inflammation of the surface of the eye
- Eyesight decrease
- Headache
- Feeling weak
- Stuffy or runny nose

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom/effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Un-common	Bradycardia/ heart rate decreased		√	
	Hypotension/ blood pressure decreased		√	

This is not a complete list of side effects. For any unexpected effects while taking **BRIMONIDINE P***, contact your doctor or pharmacist.*

HOW TO STORE IT

BRIMONIDINE P should be stored at room temperature between 15°C to 30°C (59°F-86°F). Discard unused solution at the end of treatment.

Keep out of reach of children.

REPORTING SUSPECTED SIDE EFFECTS
You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- **Report online at www.healthcanada.gc.ca/medeffect**
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
  - **Fax toll-free to 1-866-678-6789, or**
  - **Mail to: Canada Vigilance Program**
    Health Canada
    Post Locator 0701E
    Ottawa, Ontario, K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

For more information, please contact your doctor, pharmacist or other healthcare professional.

This leaflet plus the full product monograph, prepared for health professionals, can be obtained by contacting AA Pharma Inc. at:

1-877-998-9097

This leaflet was prepared by AA Pharma Inc.

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