PRODUCT MONOGRAPH

[Pr]SANDOZ BRIMONIDINE

(Brimonidine Tartrate)

Ophthalmic Solution 0.2% w/v

Relatively Selective α_2,-Adrenoceptor Agonist

Elevated lntraocular Pressure Therapy

Sandoz Canada Inc.
145, Jules-Léger
Boucherville, QC
J4B 7K8

Date of Revision: December 13, 2013

Submission Control No: 170397

Table of Contents

[Pr]SANDOZ BRIMONIDINE

Brimonidine Tartrate Ophthalmic Solution, 0.2%

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Ophthalmic	Solution, 0.2% w/v brimonidine tartrate	Contains 0.005% benzalkonium chloride as preservative *For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

Sandoz Brimonidine (brimonidine tartrate) ophthalmic solution 0.2% w/v 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 Sandoz Brimonidine 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 Sandoz Brimonidine 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

Sandoz Brimonidine 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 oral doses are approximately 830 and 330 times greater, respectively, than the maximum recommended human daily ophthalmic dosage for brimonidine tartrate ophthalmic solution (0.003 mg base/kg/day), based on a 60 kg human.

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 had minimal effect on blood pressure and heart rate of patients in clinical studies, caution should be exercised in treating patients with severe cardiovascular disease.

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

Hepatic/Biliary/Pancreatic

Brimonidine tartrate ophthalmic solution has not been studied in patients with hepatic or renal impairment; caution should be exercised in treating such patients.

Ophthalmologic

The preservative in Sandoz Brimonidine, benzalkonium chloride, may be absorbed by soft contact lenses. Patients wearing soft contact lenses should be instructed to wait at least 15 minutes after instilling Sandoz Brimonidine to insert soft contact lenses.

Delayed ocular hypersensitivity reactions have been reported with brimonidine tartrate ophthalmic solution, with some reported to be associated with an increase in intraocular pressure (IOP) (see ADVERSE REACTIONS section).

Psychiatric
Brimonidine tartrate ophthalmic solution should be used with caution in patients with depression.

Sensitivity/Resistance
Brimonidine tartrate ophthalmic solution 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 at approximately 550 and 1110 times, respectively, the maximum recommended human daily ophthalmic dosage for brimonidine tartrate ophthalmic solution based on a 60 kg human.

There are no studies of brimonidine tartrate ophthalmic solution 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. Sandoz Brimonidine should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus.

Nursing Women: It is not known whether brimonidine is excreted in human milk, although in animal studies, brimonidine has been shown to be excreted in breast milk. During treatment with Sandoz Brimonidine, 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 Sandoz Brimonidine 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 Sandoz Brimonidine 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).

Occupational Hazards
Brimonidine tartrate ophthalmic solution, 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 tartrate ophthalmic solution 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.

Based on safety data from two pivotal clinical studies and three ancillary studies conducted on brimonidine tartrate ophthalmic solution, most adverse reactions were transient and not commonly of a severity requiring discontinuation of treatment. 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

System Organ Class Preferred Terma	Brimonidine 0.2% n= <717> (%)	Timolol 0.5% n= <413> (%)
Eye disorders		
ocular hyperemia	178 (24.8%)	104 (25.2%)
burning and stinging	161 (22.5%)	180 (43.6%)
blurring	124 (17.3%)	93 (22.5%)
foreign body sensation	111 (15.5%)	69 (16.7%)
corneal staining/erosion	72 (10.0%)	48 (11.6%)
ocular allergic reactionsb	71 (9.9%)	1 (0.2%)
ocular pruritus	70 (9.8%)	42 (10.2%)
conjunctival follicles	69 (9.6%)	23 (5.6%)
photophobia	53 (7.4%)	42 (10.2%)
ocular dryness	50 (7.0%)	40 (9.7%)
eyelid erythema	44 (6.1%)	22 (5.3%)
ocular ache/pain	43 (6.0%)	18 (4.4%)
lacrimation disorder	40 (5.6%)	21 (5.1%)
conjunctival edema	38 (5.3%)	26 (6.3%)
eyelid edema	35 (4.9%)	13 (3.1%)
conjunctival blanching	27 (3.8%)	16 (3.9%)
blepharitis	26 (3.6%)	12 (2.9%)
ocular irritation	22 (3.1%)	6 (1.5%)
abnormal vision	19 (2.6%)	15 (3.6%)
conjunctival discharge	10 (1.4%)	7 (1.7%)
conjunctival papillae	7 (1.0%)	9 (2.2%)

System Organ Class Preferred Terma	Brimonidine 0.2% n= <717> (%)	Timolol 0.5% n= <413> (%)
Gastrointestinal disorders		
oral dryness	185 (25.8%)	69 (16.7%)
gastrointestinal symptoms	22 (3.1%)	14 (3.4%)
abnormal taste	10 (1.4%)	5 (1.2%)
General disorders and administration site conditions		
asthenia	20 (2.8%)	7 (1.7%)
fatigue/drowsiness	109 (15.2%)	62 (15.0%)
systemic other	32 (4.5%)	25 (6.1%)
Nervous system disorders		
headache	117 (16.3%)	83 (20.1%)
dizziness	30 (4.2%)	15 (3.6%)
Respiratory, thoracic and mediastinal disorders		
upper respiratory symptoms	43 (6.0%)	21 (5.1%)
nasal dryness	7 (1.0%)	4 (1.0%)

[a] MedDRA System Organ Class and Preferred Terms
[b] It should be noted that ocular allergic reaction includes allergic blepharitis, allergic blepharoconjunctivits, allergic conjunctivitis, allergic reaction (ocular) and follicular conjunctivitis.

Less Common Clinical Trial Adverse Drug Reactions (<1%)

Cardiac disorders: palpitations
Immune system disorders: systemic allergic reactions
Psychiatric disorders: depression

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 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 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 post-marketing 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.

Eye disorders: iritis, iridocyclitis (anterior uveitis), miosis, conjunctivitis, eyelids pruritus
Immune system disorders: hypersensitivity, skin reaction
Nervous system disorders: syncope

Vascular disorders: hypotension

The following adverse reactions have been identified during post-marketing use of brimonidine tartrate ophthalmic solution (0.15%) 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

DRUG INTERACTIONS

Overview
Brimonidine tartrate ophthalmic solution 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), anti-hypertensives 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 can lead to an interference in IOP lowering effect. No data are available on the level of circulating catecholamines after brimonidine tartrate ophthalmic solution 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, 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 1 drop of Sandoz Brimonidine in the affected eye(s) twice daily (doses taken approximately 12 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 Sandoz Brimonidine 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 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 immediately.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Brimonidine tartrate is a relatively selective alpha 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 intraocular pressure (IOP) in humans. When used as directed, brimonidine tartrate ophthalmic solution reduces elevated IOP with minimal effect on cardiovascular parameters.

Brimonidine tartrate ophthalmic solution 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 lowers IOP by reducing aqueous humor production and increasing uveoscleral outflow.

Pharmacodynamics

Brimonidine tartrate ophthalmic solution has no effect on pulmonary function or exercise induced tachycardia. The cardiovascular effects of brimonidine tartrate ophthalmic solution 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 tartrate ophthalmic solution twice daily (both eyes) in humans for 10 days, plasma concentrations were low (mean C_{max} = 0.06 ng/mL). With both brimonidine tartrate ophthalmic solution concentrations, plasma brimonidine concentrations peaked within 1 to 4 hours and declined with a systemic half-life of approximately 3 hours.

STORAGE AND STABILITY

Store at 4 - 30°C.

SPECIAL HANDLING INSTRUCTIONS

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.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Sandoz Brimonidine is supplied in white, opaque plastic Drop-Tainer® bottles containing 5 mL or 10 mL.

Each mL of Sandoz Brimonidine contains brimonidine tartrate 2.0 mg with the following non-medicinal ingredients: 0.005% benzalkonium chloride as preservative and citric acid, polyvinyl alcohol, sodium chloride, sodium citrate, hydrochloric acid and/or sodium hydroxide (to adjust pH) and purified water.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

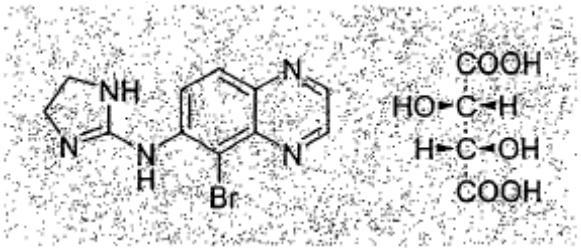
Proper name: Brimonidine tartrate

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

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

Molecular mass: 442.24 g/mol

Structural formula:



Physicochemical properties: 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 pKa 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	No. in Preferred Analysis		
103-7831	Multicentre, randomized, double-blind, parallel, active control	One drop in each eye twice daily	443	286	394	62.5 (28-84)	107/125
		B - Brimonidine 0.2%	B – 221	B – 119	B – 186	B – 62.7 (28-84)	B – 84/102
		T - Timolol 0.5%	T – 222	T – 167	T – 188	T – 62.2 (34-83)	T – 103/85
		1 year					
104-7831	Multicentre, randomized, double-blind, parallel, active control	One drop in each eye twice daily	483	305	463	62.3 (28-86)	234/229
		B - Brimonidine 0.2%	B – 292	B – 156	B – 280	B – 63.0 (28-86)	B – 138/142
		T - Timolol 0.5%	T – 191	T – 149	T – 183	T – 61.4 (33-83)	T – 96/87
		1 year					

* Uneven randomization – 3:2 ratio, brimonidine

Study results
Brimonidine tartrate ophthalmic solution 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).

The long term efficacy of brimonidine tartrate ophthalmic solution dosed b.i.d. was demonstrated in two one-year multicenter studies in subjects with open angle glaucoma or ocular hypertension. In these trials, brimonidine tartrate ophthalmic solution lowered IOP by mean values of 4.3 mmHg at trough and 6.7 mmHg at peak. IOP decreases were maintained for the duration of the studies in the majority of patients; no tachyphylaxis was observed. Nine percent of subjects were discontinued from the studies due to inadequately controlled intraocular pressure.

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, b.i.d) 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.

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 3, brimonidine is notably more alpha-2 adrenoceptor selective than clonidine and p-aminoclonidine in both radioligand binding and functional assays.

Table 3: Receptor Pharmacology of Brimonidine, Clonidine and p-Aminoclonidine

Radioligand 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)
ρ-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 4).

Table 4: The IOP Response to Chronic Administration of Brimonidine (b.i.d. 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 (mmHg) 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 b.i.d 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 4).

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 rats, no deleterious effects on the optic nerve were observed.

Human Pharmacology

Mechanism of Action

The effect of brimonidine on aqueous humor 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. Aqueous flow (Fa mcL/min) and outflow capacity (C_{fl} mcL/min/mmHg) were determined using a fluorophotometric technique. Intraocular pressure (IOP, mmHg), tonographic outflow facility (C_{ton} mcL/min/mmHg), and episcleral venous pressure (Pev, mmHg)

were also measured. Uveoscleral outflow (mcL/min) by fluorophotometry (Fu_{fl}) or tonography (Fu_{ton}) was calculated from C_{fl} or C_{ton} values, respectively.

The results of this study (mean ± SEM) are reported in Table 5. They indicate that brimonidine reduces IOP in humans by decreasing aqueous inflow and increasing uveoscleral outflow.

Table 5: Effects of Brimonidine on Aqueous Humor Dynamics

	Control Eye		Treated Eye	
	Baseline	**Day 8**	**Baseline**	**Day 8**
IOP	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 ± 0.4	8.8 ± 0.5	9.2 ± 0.3

* $p \leq 0.05$ *vs* baseline
† $p \leq 0.05$ *vs* control

Pharmacodynamics

In short term studies (up to four days) in normal healthy volunteers, brimonidine tartrate ophthalmic solution 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 b.i.d. 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 (b.i.d.), 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.

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.

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 (IV) administration. The LD_{50} or MLD values for each study are listed below:

Species	Route	LD_{50} (mg/kg)*	MLD (mg/kg)*
Mouse	Oral IV	50 50	> 8** Not performed
Rat	Oral IV	100 100-150	> 8** Not performed
Rabbit	Oral IV	Not performed Not performed	> 6 20-50
Dog	Oral IV	Not performed Not performed	0.5 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 ocularly 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 165 times the recommended ocular human dose, rats at approximately 80 times the recommended ocular human dose, rabbits at approximately 25 times the recommended ocular human dose, dogs at approximately 55 times the recommended ocular human dose and monkeys at 33 times the recommended ocular human dose. Dosage levels of approximately 330 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 3000 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 1500 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 characterized 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 characterized 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 120 times the recommended ocular human dose, dogs up to approximately 20 times the recommended ocular human dose, and monkeys up to approximately 40 times the recommended ocular human dose.

Carcinogenicity
There was no compound-related oncogenic effect observed in either mice or rats studies.

The maximal brimonidine plasma concentrations after oral administration of 2.5 mg base/kg/day to mice for 21 months correspond to approximately 77 times the human systemic exposure to brimonidine tartrate 0.2% ophthalmic solution instilled in each eye (one drop) twice daily for 10 days, and approximately 44 times the human systemic exposure to brimonidine tartrate 0.5% ophthalmic solution administered as a single dose (one drop in each eye) . After two years of oral administration at 1.0 mg base/kg/day to rats, plasma concentrations were approximately 118 times greater than those seen in humans receiving one drop of brimonidine tartrate 0.2% ophthalmic solution in each eye b.i.d. for 10 days and approximately 67 times greater than those seen in humans receiving a single dose of brimonidine tartrate 0.5% ophthalmic solution (one drop in each eye). There were no observable tumorigenic effects seen in mice or rats dosed at 2.5 mg base/kg/day (approximately 830 times the recommended human ocular dose) for up to

24 months.

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
Reproductive toxicology studies conducted with brimonidine in rats and rabbits showed that brimonidine had no adverse effects on fertility and general reproductive performance and showed no evidence of embryolethal or teratogenic activity at the dosages administered.

The mean maximal plasma brimonidine concentrations measured during the rat teratogenicity study (1.65 mg base/kg/day, orally) were approximately 333 times the human systemic exposure to brimonidine tartrate 0.2% ophthalmic solution instilled in each eye (one drop) twice daily for 10 days, and approximately 189 times the human systemic exposure to brimonidine tartrate 0.5% ophthalmic solution administered as a single dose (one drop in each eye). Mean maximal plasma brimonidine concentrations in the rabbit teratogenicity study (3.33 mg base/kg/day, orally) were approximately 24 times greater than plasma concentrations seen in humans receiving one drop of brimonidine tartrate 0.2% solution in each eye b.i.d. for 10 days and approximately 14 times greater than plasma levels seen in humans receiving a single dose of brimonidine tartrate 0.5% ophthalmic solution (one drop in each eye).

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 1100 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, et al. Therapeutic use of α-2-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.

3. David R, Spaeth GL, Clevenger CE et al. Brimonidine in the prevention of intraocular pressure elevation following argon laser trabeculoplasty. Arch Ophthalmol 1993; 111: 1387-1390.

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

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

6. 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%. lnvest Ophthalmol Vis Sci 1993; 34(4):929 (1139).

7. 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. lnvest Ophthalmol Vis Sci 1992; 33(4): 1159 (2340).

8. Toris CB, Camras CB, Yablonski ME. The effects of brimonidine on aqueous humor dynamics in human eyes. lnvest Ophthalmol Vis Sci 1994; 35(4): 2052 (3703).

9. 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. lnvest Ophthalmol Vis Sci 1991; 32(4): 988 (1572).

10. Allergan Inc., Product Monograph ALPHAGAN (brimonidine tartrate), Control No. 166703, Date of Revision October 8, 2013.

PART III: CONSUMER INFORMATION

Sandoz Brimonidine
Brimonidine tartrate 0.2%, w/v

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

ABOUT THIS MEDICATION

What the medication is used for:
Sandoz Brimonidine eye drops are used to reduce high pressure in the eye in patients with chronic open-angle glaucoma or ocular hypertension.

What it does:
Sandoz Brimonidine 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 Sandoz Brimonidine:

- 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 nonmedicinal ingredients are:
0.005% benzalkonium chloride, as preservative, citric acid, polyvinyl alcohol, purified water, sodium chloride and sodium citrate. Hydrochloric acid and/or sodium hydroxide may be added to adjust pH.

What dosage forms it comes in:
Ophthalmic solution, brimonidine tartrate 0.2%, w/v

WARNINGS AND PRECAUTIONS

Sandoz Brimonidine 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 Sandoz Brimonidine 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 Sandoz Brimonidine'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. The preservative in Sandoz Brimonidine (benzalkonium chloride) may be absorbed by soft (hydrophilic) contact lenses. Lenses should be removed prior to using Sandoz Brimonidine and kept out for 15 minutes after use.

INTERACTIONS WITH THIS MEDICATION

Drugs that may interact with Sandoz Brimonidine 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 Sandoz Brimonidine.

PROPER USE OF THIS MEDICATION

Usual adult dose:
Normally, you should put one drop of Sandoz Brimonidine in each eye that needs treatment, twice every day, about 12 hours apart, following the instructions for use below.

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

Follow the following steps to help you use Sandoz Brimonidine 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.

Sandoz Brimonidine contains a preservative called benzalkonium chloride which may discolour soft contact lenses. If you wear contact lenses, remove them before using Sandoz Brimonidine. Wait 15 minutes after using the drops before you put your lenses back in.

Always use Sandoz Brimonidine exactly as your doctor has instructed you. If you use Sandoz Brimonidine with another eye drop, leave at least five minutes between putting in Sandoz Brimonidine 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. **Do not 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 Sandoz Brimonidine. If these persist or cause you concern, consult your doctor.

Very common:
- Dry mouth
- Irritation of the eye (eye redness, burning, stinging, a feeling of something in the eye)
- Blurred vision
- Headache
- Tiredness, sleepiness or drowsiness

Common:
- Local irritation (inflammation and swelling of the eyelid, pain and tearing)
- Sensitivity to light
- Erosion on the surface of the eye and staining
- Eye dryness
- Abnormal vision
- Dizziness
- Cold-like symptoms
- Symptoms involving the stomach and digestion
- Abnormal taste
- General weakness

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	
Uncommon	Bradycardia/ heart rate decreased		✓	
	Hypotension/ blood pressure decreased		✓	

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

HOW TO STORE IT

Sandoz Brimonidine should be stored at 4°C to 30°C.

Do not use the drops after the expiry date (marked "Exp") on the bottle and the box.

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
    Postal 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

This document plus the full product monograph, prepared for health professionals can be found by contacting the sponsor, Sandoz Canada Inc., at:

1-800-361-3062

or by written request at:
145 Jules-Léger
Boucherville QC
J4B 7K8

Or by e-mail at :
medinfo@sandoz.com

This leaflet was prepared by Sandoz Canada Inc.

Last revised: December 13, 2013