PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr]SANDOZ BRIMONIDINE

Brimonidine Tartrate Ophthalmic Solution

Solution, 0.2% w/v, for ophthalmic use

Relatively Selective α_2-Adrenoceptor Agonist

ATC Code: S01EA05

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RECENT MAJOR LABEL CHANGES

None at the time of the most recent authorization.

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

Sandoz Brimonidine (brimonidine tartrate) is indicated for:

- the control of intraocular pressure in patients with chronic open-angle glaucoma or ocular hypertension.

1.1 Pediatrics

Pediatrics (< 18 years of age): The safety and efficacy of brimonidine tartrate has not been established in pediatric patients; therefore, Health Canada has not authorized an indication for pediatric use. Several serious adverse reactions have been reported in association with the administration of brimonidine tartrate ophthalmic solution 0.2% in pediatric populations. See 2 CONTRAINDICATIONS, 7.1.3 Pediatrics and 8.2.1 Clinical Trial Adverse Reactions – Pediatrics.

1.2 Geriatrics

Geriatrics (> 65 years of age): No overall difference in safety and effectiveness has been observed between elderly and other adult patients.

2 CONTRAINDICATIONS

Sandoz Brimonidine is contraindicated in:

- Patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or components of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.
- Patients receiving monoamine oxidase (MAO) inhibitor therapy.
- Neonates and infants (children under the age of 2 years).

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- Patients should be advised that if they have ocular surgery or develop any type of ocular condition, they should immediately seek their doctor's advice concerning the continued use of the present bottle.

4.2 Recommended Dose and Dosage Adjustment

- The recommended dose is 1 drop of Sandoz Brimonidine in the affected eye(s) twice daily (BID) (doses taken approximately 12 hours apart).

Health Canada has not authorized an indication for pediatric use.

4.4 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 and subsequent loss of vision may result from using contaminated solutions.

Patients Wearing Soft Contact Lenses:

Lenses should be removed prior to the application of Sandoz Brimonidine and not re-inserted earlier than 15 minutes after administration.

4.5 Missed Dose

A missed dose should be applied as soon as the patient remembers. The regular dosing schedule should then be resumed with the next dose. Patients should not apply more than one dose at a time in an effort to catch up on missed doses.

5 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 patient's 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 as part of medical treatment of congenital glaucoma or by accidental oral ingestion. See 2 CONTRAINDICATIONS.

For management of a suspected drug overdose, including accidental ingestion, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Ophthalmic	Solution, 0.2% w/v brimonidine tartrate	Contains 0.005% benzalkonium chloride as preservative, citric acid, polyvinyl alcohol, sodium chloride, sodium citrate, hydrochloric acid and/or sodium hydroxide (to adjust pH) and purified water.

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

7 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 (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 the dominant lethal assay.

Cardiovascular

Although brimonidine tartrate 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.

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

Driving and Operating Machinery

Sandoz Brimonidine, 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.

Sandoz Brimonidine 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.

Hepatic/Biliary/Pancreatic

Brimonidine tartrate has not been studied in patients with hepatic 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, with some reported to be associated with an increase in intraocular pressure (IOP). See 8 ADVERSE REACTIONS.

Psychiatric

Sandoz Brimonidine should be used with caution in patients with depression.

Renal

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

Sensitivity/Resistance

Sandoz Brimonidine should be used with caution in patients with known hypersensitivity to other alpha-adrenoceptor agonists.

7.1 Special Populations

7.1.1 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, respectively), were administered at approximately 550 and 1110 times, respectively, the maximum recommended human daily ophthalmic dosage for brimonidine tartrate based on a 60 kg human.

There are no studies of brimonidine tartrate 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.

7.1.2 Breast-feeding

It is not known whether brimonidine is excreted in human milk; however 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.

7.1.3 Pediatrics

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 2 CONTRAINDICATIONS and 8.2.1 Clinical Trial Adverse Reactions – Pediatrics.

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 the pediatric population. See 8.2.1 Clinical Trial Adverse Reactions – Pediatrics.

7.1.4 Geriatrics

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.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

Two 12-month Phase 3 clinical studies and 3 ancillary clinical studies were conducted with brimonidine tartrate. Based on the clinical data, the most commonly reported adverse drug reactions were oral dryness (25.8%), ocular hyperemia (24.8%), burning and stinging (22.5%), blurring (17.3%), headache (16.3%), foreign body sensation (15.5%), fatigue/drowsiness (15.2%). Ocular allergic reactions (including allergic blepharoconjunctivitis, allergic conjunctivitis, follicular conjunctivitis) were the most frequent cause for discontinuation in the clinical trials (8.5%). Oral dryness and ocular hyperemia, although frequently reported, were infrequent causes for discontinuation at 1.1% and < 1%, respectively. Serious adverse events (AEs) were reported for a total of 23 patients (3.0%); none of the serious AEs were ocular and none were considered treatment related.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. Therefore, 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 reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

Table 2 – Treatment-Related Adverse Reactions Occurring at ≥1% with Brimonidine tartrate

	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 reactions[a]	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%)
Gastrointestinal		
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		
fatigue/drowsiness	109 (15.2%)	62 (15.0%)
systemic other	32 (4.5%)	25 (6.1%)
asthenia	20 (2.8%)	7 (1.7%)
Nervous system disorders		

	Brimonidine 0.2% n= 717 (%)	Timolol 0.5% n= 413 (%)
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] It should be noted that ocular allergic reaction includes allergic blepharitis, allergic blepharoconjunctivits, allergic conjunctivitis, allergic reaction (ocular) and follicular conjunctivitis.

Based on safety data from two pivotal clinical studies and three ancillary studies conducted on brimonidine tartrate, 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 2 above using MedDRA System Organ Class.

8.2.1 Clinical Trial Adverse Reactions – Pediatrics

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 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. See 2 CONTRAINDICATIONS and 7.1.3 Pediatrics.

8.3 Less Common Clinical Trial Adverse Reactions

Cardiac disorders: palpitations

Immune system disorders: systemic allergic reactions

Psychiatric disorders: depression

8.5 Post-Market Adverse Reactions

The following adverse reactions have been identified during post-marketing use of brimonidine tartrate ophthalmic solution 0.2% w/v 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

Nervous system disorders: syncope

Psychiatric disorders: depression

Skin and subcutaneous tissue disorders: skin reaction

Vascular disorders: hypotension

The following adverse reactions have been identified during post-marketing use of brimonidine tartrate ophthalmic solution 0.15% w/v 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

Immune system disorders: hypersensitivity

Nervous system disorders: dizziness, somnolence

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

Brimonidine tartrate 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.

9.3 Drug-Behavioural Interactions

No formal drug-behavioural interaction studies were conducted with brimonidine tartrate.

9.4 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 can lead to an interference in IOP lowering effect. No data are available on the level of circulating catecholamines after brimonidine tartrate 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, the possibility of an additive or potentiating effect with central nervous system (CNS) depressants (e.g., alcohol, barbiturates, opiates, sedatives or anesthetics) should be considered.

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 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, Sandoz Brimonidine reduces elevated IOP with minimal effect on cardiovascular parameters.

Sandoz Brimonidine 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. Sandoz Brimonidine lowers IOP by reducing aqueous humor production and increasing uveoscleral outflow.

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 BID application of one drop of brimonidine tartrate 0.2% to one eye and vehicle to the other eye, in a double-blind fashion. The results of this study (mean ± SEM) are reported in Table 3. They indicate that brimonidine reduces IOP in humans by decreasing aqueous inflow and increasing uveoscleral outflow.

Table 3 – 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
Fa = aqueous flow (mcL/min)
C_{fl} = outflow capacity (mcL/min/mmHg)
IOP = intraocular pressure (mmHg)
C_{ton} = tonographic outflow facility (mcL/min/mmHg)
Pev = episcleral venous pressure (mmHg)
Fu_{fl} = uveoscleral outflow by fluorophotometry (mcL/min)
Fu_{ton} = uveoscleral outflow by tonography (mcL/min)

10.2 Pharmacodynamics

Brimonidine tartrate has no effect on pulmonary function or exercise-induced tachycardia. The cardiovascular effects of brimonidine tartrate 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.

In short-term studies (up to four days) in normal healthy volunteers, brimonidine tartrate ophthalmic solution preserved with benzalkonium chloride lowered IOP 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 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.

10.3 Pharmacokinetics

Table 4 – Summary of Brimonidine Pharmacokinetic Parameters in Healthy Volunteers

	C_{max} (ng/mL)	T_{max} (hr)	$t_{1/2}$ (hr)	$AUC_{0\text{-}12hr}$
BID for 10 days mean	0.0585	1-4	3	0.309

Absorption

After ocular administration of brimonidine tartrate BID (both eyes) in humans for 10 days, plasma concentrations were low (mean C_{max} = 0.06 ng/mL). With both brimonidine tartrate concentrations, plasma brimonidine levels peaked within 1 to 4 hours and declined with a systemic half-life of approximately 3 hours.

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 Cmax and AUC0-4 were approximately 0.1 ng/mL and 0.5 ng·hr/mL, respectively. The mean Tmax 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 t1/2 ranged from 2 to 5 hours (mean = 3.3 hours).

Metabolism

Brimonidine is metabolized primarily by the liver.

Elimination

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

Special Populations and Conditions

- **Geriatrics:** 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.

11 STORAGE, STABILITY AND DISPOSAL

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

Keep out of sight and reach of children.

12 SPECIAL HANDLING INSTRUCTIONS

Patients should be advised to avoid touching the tip of the bottle to the eye or any surface, as this may contaminate the solution. Refer to 4.4 Administration for more detailed information.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

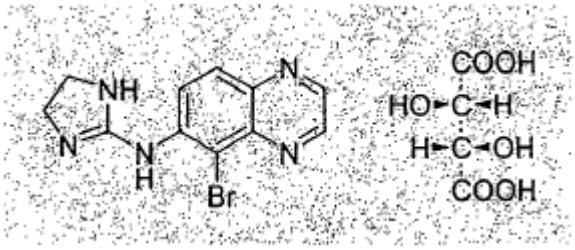
Drug Substance

Proper name: Brimonidine tartrate

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

Molecular formula and molecular mass: $C_{11}H_{10}BrN_5 \bullet C_4H_6O_6$ and 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.

14 CLINICAL TRIALS

14.1 Clinical Trial by Indication

Control of Intraocular Pressure

Table 5 – Summary of patient demographics for clinical trials in the control of intraocular pressure

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)			Mean age (Range)	Sex
			No. Entered	No. Completed	No. in Preferred Analysis		

Study	Study	Dosage, route	Study subjects (n)			Mean	Sex
103-7831	Multicentre, randomized, double-blind, parallel, active control	One drop in each eye twice daily B - Brimonidine 0.2% T - Timolol 0.5% 1 year	443 B – 221 T – 222	286 B – 119 T – 167	394 B – 186 T – 188	62.5 (28-84) B – 62.7 (28-84) T – 62.2 (34-83)	107/125 B – 84/102 T – 103/85
104-7831	Multicentre, randomized, double-blind, parallel, active control	One drop in each eye twice daily B - Brimonidine 0.2% T - Timolol 0.5% 1 year	483 B – 292 T – 191	305 B – 156 T – 149	463 B – 280 T – 183	62.3 (28-86) B – 63.0 (28-86) T – 61.4 (33-83)	234/229 B – 138/142 T – 96/87

* Uneven randomization – 3:2 ratio, brimonidine

Table 6 – Results of studies 103-7831 and 104-7831 in the control of intraocular pressure – intraocular pressure values (mm Hg) phase 3 studies (preferred analysis)

		Study 103-7831		Study 104-7831	
		Brimonidine tartrate (0.2%) n = 186	**Timolol (0.5%) n = 188**	**Brimonidine tartrate (0.2%) n = 274**	**Timolol (0.5%) n = 180**
Baseline	**Hour-0**				
	Mean	25.80	25.87	25.96	25.85
	SD	2.31	2.81	3.01	2.80
	Min / Max	23.0 / 32.0	23.0 / 34.0	22.5 / 34.5	23.0 / 34.0
	Hour-2				
	Mean	24.20	24.19	25.06	24.73
	SD	3.45	3.35	3.38	3.12
	Min / Max	15.0 / 34.5	12.5 / 34.0	17.5 / 36.0	-19.5 / 2.0
Month-12	**Hour-0**				
	Mean change from baseline	-3.67	-5.88	-3.80	-5.72
	SD	3.98	3.38	3.73	3.34
	Min / Max	-11.5 / 8.5	-16.0 / 6.5	-12.5 / 6.5	-13.0 / 5.5
	P-value[a]	<0.001	<0.001	<0.001	<0.001
	Hour-2				
	Mean change from baseline	-5.30	-5.61	-7.00	-5.49
	SD	3.79	3.62	4.18	3.70
	Min / Max	-13.5 / 8.0	-14.0 / 4.5	-20.5 / 2.5	-12.5 / 6.0
	P-value[a]	<0.001	<0.001	<0.001	<0.001

		Study 103-7831		Study 104-7831	
		Brimonidine tartrate (0.2%) n = 186	**Timolol (0.5%) n = 188**	**Brimonidine tartrate (0.2%) n = 274**	**Timolol (0.5%) n = 180**
Overall[b]		-4.32	-6.33	-6.81	-5.91

n = number of patients at baseline; SD = standard deviation
a = within-group analysis of changes from baseline using paired t-test
b = Least-squares means for IOP changes over the 12 months of study

Brimonidine tartrate lowers IOP 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 dosed BID was demonstrated in two one-year multicenter studies in subjects with open angle glaucoma or ocular hypertension. In these trials, brimonidine tartrate 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 IOP.

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.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General 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	50	$>$ 8**
	IV*	50	Not performed
Rat	Oral	100	$>$ 8**
	IV	100-150	Not performed
Rabbit	Oral	Not performed	$>$ 6
	IV	Not performed	20-50
Dog	Oral	Not performed	0.5
	IV	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 MLD.

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), 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% instilled in each eye (one drop) BID for 10 days, and approximately 44 times the human systemic exposure to brimonidine tartrate 0.5% 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% in each eye BID for 10 days, and approximately 67 times greater than those seen in humans receiving a single dose of brimonidine tartrate 0.5% (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.

Genotoxicity: 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 CHO cells, cytogenic studies in mice and the dominant lethal assay.

Reproductive and Developmental Toxicology: 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% instilled in each eye (one drop) BID for 10 days, and approximately 189 times the human systemic exposure to brimonidine tartrate 0.5% 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% in each eye BID for 10 days, and approximately 14 times greater than plasma levels seen in humans receiving a single dose of brimonidine tartrate 0.5% (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.

17 SUPPORTING PRODUCT MONOGRAPHS

1. PrALPHAGAN®, brimonidine tartrate ophthalmic solution, 0.2% w/v, submission control 267088, Product Monograph, AbbVie Corporation. (SEP 29, 2022)

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr]Sandoz Brimonidine

Brimonidine Tartrate Ophthalmic Solution

Read this carefully before you start taking **Sandoz Brimonidine** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **Sandoz Brimonidine**.

What is Sandoz Brimonidine used for?

- Sandoz Brimonidine eye drops are used to reduce high pressure in the eye in adult patients with:
  - chronic open-angle glaucoma (a condition that causes damage to the optic nerve of your eye).
  - ocular hypertension (high pressure in the eye).

How does Sandoz Brimonidine work?

Sandoz Brimonidine is an 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. It contains a preservative.

What are the ingredients in Sandoz Brimonidine?

Medicinal ingredient: brimonidine tartrate

Non-medicinal ingredients: 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.

Sandoz Brimonidine comes in the following dosage forms:

Ophthalmic solution, 0.2% w/v

Do not use Sandoz Brimonidine if:

- you are allergic to brimonidine tartrate, any of the other ingredients, or to any component of the Sandoz Brimonidine container (See **What are the ingredients in Sandoz Brimonidine?**).
- you are receiving monoamine oxidase (MAO) inhibitor therapy (used to treat depression).
- Sandoz Brimonidine should not be used in children under the age of 2 years.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Sandoz Brimonidine. Talk about any health conditions or problems you may have, including if you:

- are breastfeeding a baby, pregnant or intend to become pregnant.
- have or have had heart and blood vessel problems.
- have or have had circulation problems which make the toes and fingers numb and pale. This is called Raynaud's phenomenon.
- have or have had low blood pressure.
- are taking or intend to take other medicines. This is particularly important if you are taking medicine to lower blood pressure or to treat heart disease.
- have or have had liver problems.
- have or have had kidney problems.
- have or have had depression.
- have or have had eye surgery.
- develop an eye condition due to infection or injury.
- wear contact lenses. The preservative in Sandoz Brimonidine may be absorbed by soft (hydrophilic) contact lenses. Lenses should be removed before using Sandoz Brimonidine and kept out for 15 minutes after use.

Other warnings you should know about:

Immediately tell your healthcare professional if you:

- have or have had eye surgery.
- develop an eye condition due to infection or injury.

Ask your healthcare professional for their advice on whether you should continue to use the Sandoz Brimonidine bottle.

Driving and using machines:

Sandoz Brimonidine may cause drowsiness and fatigue or blurred vision. Do not drive, use heavy machinery or participate in dangerous activities or activities requiring you to be alert, until these conditions have passed.

Children (2-18 years of age): The use of Sandoz Brimonidine is currently not recommended in children, as several serious side effects have been reported with the use of brimonidine tartrate ophthalmic solution 0.2% in children.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with Sandoz Brimonidine:

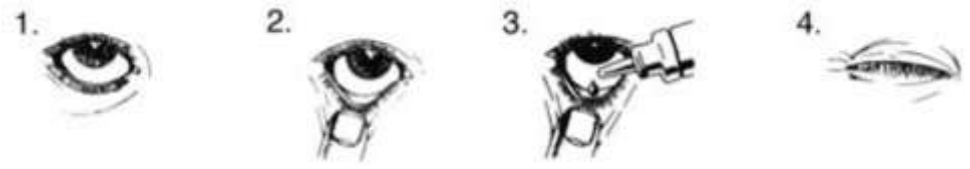
- antihypertensives (medicines used to treat high blood pressure).
- cardiac glycoside (medicines used to treat heart failure and irregular heartbeats).
- central nervous system depressants (alcohol, barbiturates, opiates, sedatives, or anesthetics).
- clonidine (medicine used to treat high blood pressure and attention deficit hyperactivity disorder [ADHD]).
- heart and blood pressure medications such as alpha-agonists.
- medication such as beta-blockers (ophthalmic and/or systemic, used to treat high blood pressure and irregular heartbeats).
- tricyclic antidepressants (medicines used to treat depression).

How to take Sandoz Brimonidine:

- You must not use the bottle if the tamper-proof seal on the bottle neck is broken before you first use it.
- Sandoz Brimonidine contains a preservative called benzalkonium chloride which may change the colour of 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 healthcare professional has told you to.
- If you use Sandoz Brimonidine with other eye drops, wait at least five minutes between putting in Sandoz Brimonidine and 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.

Follow the steps below to help you use Sandoz Brimonidine properly:

1. Wash your hands. Tilt your head back and look at the ceiling. (See image 1)
2. Gently pull down the lower eyelid to create a small pocket. (See image 2)
3. Turn the bottle upside down and squeeze it gently to release one drop into the eyelid pocket. If a drop misses your eye, try again. (See image 3)
4. Let go of the lower lid and close your eye for 30 seconds. (See image 4)



5. Repeat steps 1 – 4 in the other eye if both eyes need treatment.

Usual dose:

Following the instructions for use above, put one drop of Sandoz Brimonidine in the affected eye, twice daily, about 12 hours apart.

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.

If you think you, or a person you are caring for, have taken too much Sandoz Brimonidine contact a healthcare professional, 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 healthcare professional. Do not try to catch up on missed drops by applying more than one dose at a time.

What are possible side effects from using Sandoz Brimonidine?

These are not all the possible side effects you may have when taking Sandoz Brimonidine. If you experience any side effects not listed here, tell your healthcare professional.

- abnormal taste
- abnormal vision
- allergic reaction
- blurred vision
- cold-like symptoms
- constriction of eye's pupil
- depression
- dizziness
- drowsiness
- dry mouth
- dry nose
- erosion on the surface of the eye and staining
- eye discharge
- eye irritation
- eye dryness
- fainting
- general weakness
- headache
- irritation of the eye (eye redness, burning, stinging, a feeling of something in the eye)
- itchy eyes
- local irritation (inflammation and swelling of the eyelid, pain and tearing)
- sensitivity to light

- skin reaction
- symptoms involving the stomach and digestion
- swelling of eye's pupil
- tiredness or sleepiness

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
UNKNOWN			
Bradycardia (abnormally slow heartbeat)		✓	
Hypotension (low blood pressure): dizziness, fainting, light-headedness, blurred vision, nausea, vomiting, fatigue (may occur when you go from lying or sitting to standing up)		✓	
Tachycardia (abnormally fast heartbeat): dizziness, light headedness, shortness of breath, racing heart		✓	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

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 and sight of children.

If you want more information about Sandoz Brimonidine:

- Talk to your healthcare professional.
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website www.sandoz.ca or by calling 1-800-361-3062.

This leaflet was prepared by Sandoz Canada Inc.

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