PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

Pr SANDOZ BRINZOLAMIDE

Brinzolamide Ophthalmic Suspension

1% w/v

Elevated Intraocular Pressure Therapy
(Topical Carbonic Anhydrase Inhibitor)

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[Pr] SANDOZ BRINZOLAMIDE

Brinzolamide Ophthalmic Suspension

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Non-medicinal Ingredients
Ophthalmic (topical)	Ophthalmic suspension/ brinzolamide 0.1% w/v	Benzalkonium chloride as preservative *For a complete listing see DOSAGE FORMS, COMPOSITION AND PACKAGING section.*

INDICATIONS AND CLINICAL USE

Sandoz Brinzolamide (brinzolamide ophthalmic suspension) is indicated in the treatment of elevated intraocular pressure (IOP) in adult patients with ocular hypertension or open-angle glaucoma.

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

Pediatrics (< 18 years of age):
Sandoz Brinzolamide is not recommended in children or adolescents. The safety and effectiveness of Sandoz Brinzolamide in pediatric patients < 18 years of age have not been established.

CONTRAINDICATIONS

Sandoz Brinzolamide is contraindicated in patients with:

- Hypersensitivity to brinzolamide or to any ingredient in the formulation or component of the container. For a complete listing, see the DOSAGE FORMS, COMPOSITION AND PACKAGING section of this document.
- Hypersensitivity to sulfonamides.
- Severe renal impairment.
- Hyperchloremic acidosis.

No studies have been conducted with brinzolamide suspension in patients with hepatic or renal impairment, or in patients with hyperchloremic acidosis. Since brinzolamide and its metabolite are excreted predominantly by the kidney, Sandoz Brinzolamide suspension is, therefore, contraindicated in patients with severe renal impairment (CrCl < 30 mL/min) or hypercholermic acidosis.

The concomitant administration of Sandoz Brinzolamide and oral carbonic anhydrase inhibitors is not recommended due to potential additive systemic effects of carbonic anhydrase inhibition.

WARNINGS AND PRECAUTIONS

General

FOR TOPICAL OPHTHALMIC USE ONLY.

Like all other topically applied ophthalmic agents, brinzolamide, the active ingredient of Sandoz Brinzolamide, is absorbed systemically.

Sandoz Brinzolamide is not recommended during pregnancy or breastfeeding or in women of child-bearing potential not using contraception (see Special Populations section below).

Sandoz Brinzolamide contains brinzolamide, a sulfonamide. The same types of adverse reactions that are attributable to sulfonamides may occur with topical administration of Sandoz Brinzolamide. Hypersensitivity reactions common to all sulfonamide derivatives can occur in patients receiving Sandoz Brinzolamide. Fatalities have occurred, although rarely, due to severe reactions to sulfonamides including Stevens-Johnson syndrome, toxic epidermal necrolysis, fulminant hepatic necrosis, agranulocytosis, aplastic anemia, and other blood dyscrasias. Sensitization may occur when a sulfonamide is re-administered irrespective of the route of administration. If signs of serious reactions or hypersensitivity occur, discontinue the use of Sandoz Brinzolamide.

Acid-base disturbances have been reported with oral carbonic anhydrase inhibitors. Caution is advised when using Sandoz Brinzolamide in patients with mild to moderate renal impairment because of the possible risk of metabolic acidosis. Sandoz Brinzolamide is contraindicated in patients with severe renal impairment (see CONTRAINDICATIONS).

There is a potential for an additive effect on the known systemic effects of carbonic anhydrase inhibition in patients receiving an oral carbonic anhydrase inhibitor and Sandoz Brinzolamide. The concomitant administration of Sandoz Brinzolamide and oral carbonic anhydrase inhibitors is not recommended.

The management of patients with acute angle-closure glaucoma requires therapeutic interventions in addition to ocular hypotensive agents. Sandoz Brinzolamide is not recommended for use in patients with acute angle-closure glaucoma due to a lack of studies in such patients.

Hepatic/Biliary/Pancreatic
Brinzolamide suspension has not been studied in patients with hepatic impairment and therefore, should be used with caution in such patients.

Neurologic
Carbonic anhydrase inhibitors can impair the ability to perform tasks requiring mental alertness and/or physical coordination. As brinzolamide suspension is absorbed systematically, caution is advised when using Sandoz Brinzolamide in patients requiring mental alertness and/or physical coordination.

Ophthalmologic
The possible role of brinzolamide on corneal endothelial functions has not been investigated in patients with compromised corneas (particularly in patients with low endothelial counts). Specially, patients wearing contact lenses have not been studied, and careful monitoring of these patients when using brinzolamide is recommended since carbonic anhydrase inhibitors may affect corneal hydration and wearing contact lenses might increase the risk for the cornea. Likewise, in other cases of compromised corneas, such as patients with diabetes mellitus or corneal dystrophies, careful monitoring is recommended.

Sandoz Brinzolamide contains the preservative benzalkonium chloride, which may cause eye irritation and is known to discolour soft contact lenses. Contact with soft contact lenses is to be avoided. Patients must be instructed to remove contact lenses prior to instillation of Sandoz Brinzolamide and wait at least 15 minutes after instillation before re-inserting contact lenses.

Benzalkonium chloride has been reported to cause punctate keratopathy and/or toxic ulcerative keratopathy. Close monitoring is required with frequent or prolonged use.

Sandoz Brinzolamide may temporarily result in blurred vision following dosing. Care should be exercised in operating machinery or driving a motor vehicle.

Renal
Sandoz Brinzolamide is contraindicated in patients with severe renal impairment. Caution is advised when using Sandoz Brinzolamide in patients with mild to moderate renal impairment.

Sexual Function/Reproduction
The effect of Sandoz Brinzolamide on human fertility is unknown. Animal studies with brinzolamide demonstrated no effect on fertility (see TOXICOLOGY, Reproduction and Teratology).

Special Populations

Pregnant Women: Sandoz Brinzolamide is not recommended during pregnancy or in women of child-bearing potential not using contraception.

No adequate studies with brinzolamide have been conducted in pregnant and breast-feeding women. Development toxicity with brinzolamide was observed in animal studies. Orally

administered brinzolamide increased the number of fetal variations, such as accessory skull bones, in rabbits and decreased body weights of fetuses in rats. No treatment-related malformations were seen (see TOXICOLOGY, Reproduction and Teratology).

Nursing Women: Sandoz Brinzolamide should not be used by women nursing neonates/infants.

It is not known whether topical brinzolamide is excreted in human milk; however, a risk to the nursing child cannot be excluded.

In a study of brinzolamide in lactating rats, decreases in body weight gain in offspring at an oral dose of 15 mg/kg/day (312 times the recommended human ophthalmic dose). Following oral administration of ^{14}C-brinzolamide to lactating rats, radioactivity was found in milk at concentrations below those in the blood and plasma.

Pediatrics (< 18 years of age): The safety and effectiveness of brinzolamide suspension in pediatric patients < 18 years of age have not been established.

Geriatrics (> 65 years of age): In well-controlled clinical studies of brinzolamide suspension, the probability of having an adverse reaction was independent of age. No difference in patients experiencing adverse reactions was noted in patients less than 65 years of age, between 65 and 75 years of age, and greater than 75 years of age.

ADVERSE REACTIONS

Clinical Trial Adverse Drug Reactions

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

In well-controlled clinical studies of brinzolamide 1% ophthalmic suspension, adverse reactions related to brinzolamide were generally mild to moderate and usually did not lead to discontinuation of therapy. The most frequently reported ocular adverse reaction was blurred vision (5%). Dysgeusia was the most frequently reported systemic adverse reaction (5.6%). Adverse reactions with a frequency ≥ 1% are presented in Table 1.

Table 1 - Treatment-Related Adverse Reactions (≥ 1%)

MedDRA Preferred Term (v15.1)	**Brinzolamide 1% N=1173 (%)**	**Placebo N=101 (%)**
Eye disorders		
Vision Blurred	5.0	2.0
Ocular Discomfort	2.6	3.0
Foreign Body Sensation in eyes	1.8	0
Dry Eye	1.2	1.0
Ocular Hyperemia	1.1	1.0
Eye Pain	1.0	1.0
Nervous system disorders		
Headache	1.5	1.0
Gastrointestinal disorders		
Dysgeusia	5.6	1.0

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

Eye disorders: abnormal vision, blepharitis, conjunctivitis, eye discharge, eye fatigue, eyelid margin crusting, eye pruritus, lacrimation increased (tearing), keratitis, sticky sensation;
Gastrointestinal disorders: dry mouth, dyspepsia, nausea;
Nervous system disorders: dizziness, paresthesia;
Psychiatric disorders: depression;
Respiratory, thoracic and mediastinal disorders: bronchitis, dyspnea, pharyngitis, rhinitis;
Skin and subcutaneous tissue disorders: alopecia, dermatitis.

Post-Market Adverse Drug Reactions

The following adverse reactions were identified from subsequent clinical trials:
Cardiac disorders: angina pectoris, heart rate irregular;
Ear and labyrinth disorders: tinnitus;
Eye disorders: asthenopia, conjunctivitis allergic, corneal edema, corneal erosion, diplopia, hypoesthesia eye, periorbital edema, photophobia, photopsia, punctate keratitis, visual acuity reduced;
Gastrointestinal disorders: abdominal discomfort, diarrhea;
General disorders and administration site conditions: asthenia, chest pain, fatigue, feeling jittery, irritability;
Nervous system disorders: memory impairment, somnolence;
Psychiatric disorders: insomnia;
Respiratory, thoracic and mediastinal disorders: bronchial hypersensitivity, cough, epistaxis, nasal congestion, nasal dryness, oropharyngeal pain, rhinorrhea, sinus congestion, throat irritation, upper airway cough syndrome, upper airway tract congestion;
Skin and subcutaneous tissue disorders: pruritus generalised, urticaria.

The following adverse reactions were identified via spontaneous post-market reporting:
Metabolism and nutrition disorders: decreased appetite;
Musculoskeletal and connective tissue disorders: arthralgia;
Nervous system disorders: hypoesthesia;
Vascular disorders: blood pressure decreased.

DRUG INTERACTIONS

Drug-Drug Interactions

No specific drug interaction studies have been performed with brinzolamide suspension.

Sandoz Brimzolamide contains brinzolamide, a carbonic acid inhibitor. Acid-base disturbances have been reported with oral carbonic anhydrase inhibitors. The potential for interactions must be considered in patients receiving Sandoz Brinzolamide.

The cytochrome P-450 isozymes responsible for metabolism of brinzolamide include CYP3A4 (main), CYP2A6, CYP2B6, CYP2C8 and CYP2C9. It is expected that inhibitors of CYP3A4, such as ketoconazole, itraconazole, clotrimazole, ritonavir and troleandomycin, will inhibit the metabolism of brinzolamide by CYP3A4. Caution is advised if CYP3A4 inhibitors are given concomitantly. Brinzolamide is not an inhibitor of cytochrome P-450 isozymes.

Concomitant use of salicylates (e.g. acetylsalicylic acid) with Sandoz Brinzolamide is not recommended. Sandoz Brinzolamide may lead to decreased efficacy of the salicylate, CNS toxicity, metabolic acidosis and other adverse reactions. These alterations were not observed in clinical trials with brinzolamide ophthalmic suspension 1%; however, in patients treated with oral carbonic anhydrase inhibitors, rare cases of acid-base alterations have occurred with high dose salicylate therapy.

Concomitant use of oral carbonic anhydrase inhibitors and Sandoz Brinzolamide is not recommended. There is a potential for an additive effect on the known systemic effects of carbonic anhydrase inhibition in patients receiving an oral carbonic anhydrase inhibitor and brinzolamide eye drops.

DOSAGE AND ADMINISTRATION

Recommended Dose

Monotherapy:

When used as a monotherapy, the recommended starting adult dose is 1 drop of Sandoz Brinzolamide 1% Ophthalmic Suspension in the affected eye(s) two times daily. If the clinical response is not adequate after 4 weeks, the dosage may be increased to 1 drop three times daily.

Adjunctive Therapy with Beta-Blockers:

Sandoz Brinzolamide suspension may be used as adjunctive therapy with ophthalmic beta-blockers (see PHARMACOLOGY, Clinical Studies).

When Sandoz Brinzolamide is used concomitantly with beta-blockers, the recommended dose is the same as when it is used as a monotherapy. The drugs should be administered at least ten minutes apart.

Missed Dose
If a dose is missed, a single drop should be applied as soon as possible before reverting to the regular routine. Do not use a double dose to make up for a missed dose.

Administration
Shake well before use.

Nasolacrimal occlusion or gently closing the eyelid for two minutes after instillation is recommended. This may reduce the systemic absorption of medications administered via the ocular route and result in a decrease in systemic adverse events.

If more than one topical ophthalmic medicinal product is being used, the medicines must be administered at least 10 minutes apart.

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. Do not use suspension if the bottle is cracked or damaged in any way.

OVERDOSAGE

No data are available in humans with regards to overdosage by accidental or deliberate ingestion of brinzolamide suspension.

If overdose with Sandoz brinzolamide occurs, treatment should be symptomatic and supportive. Electrolyte imbalance, development of an acidotic state, and possible nervous system effects may occur. Serum electrolyte levels (particularly potassium) and blood pH levels should be monitored.

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

ACTION AND CLINICAL PHARMACOLOGY

Sandoz Brinzolamide is a carbonic anhydrase inhibitor formulated for topical ophthalmic use.

Carbonic anhydrase (CA) is an enzyme found in many tissues of the body including the eye. It catalyzes the reversible reaction involving the hydration of carbon dioxide and the dehydration of carbonic acid. In humans, CA exists as a number of isoenzymes, the most active being carbonic anhydrase II (CA-II), found primarily in red blood cells (RBCs), but also in other tissues. Inhibition of CA in the ciliary processes of the eye decreases aqueous humor secretion, presumably by slowing the formation of bicarbonate ions with subsequent reduction in sodium and fluid transport. The result is a reduction in intraocular pressure (IOP).

Following topical ocular administration, brinzolamide is absorbed into the systemic circulation. Due to its high affinity for CA-II, brinzolamide distributes extensively into the RBCs and exhibits a long half-life in whole blood (approximately 111 days). In humans, the metabolite N-desethyl brinzolamide is formed, which also binds to CA and accumulates in RBCs. This metabolite binds mainly to carbonic anhydrase I (CA-I) in the presence of brinzolamide. In plasma, both parent brinzolamide and N-desethyl brinzolamide concentrations are low and generally below assay quantitation limits (<10 ng/mL). Binding to plasma proteins is not extensive (about 60%). Brinzolamide is eliminated predominantly in the urine as unchanged drug. N-Desethyl brinzolamide is also found in the urine along with trace concentrations (<1% of the dose) of the N-desmethoxypropyl and O-desmethyl metabolites.

STORAGE AND STABILITY

Store Sandoz Brinzolamide at 4-30°C (36-86°F). Keep bottle tightly closed when not in use. Keep out of the reach and sight of children.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Sandoz Brinzolamide is supplied as a sterile, aqueous suspension of brinzolamide which has been formulated to be readily suspended and slow settling following shaking. The pH has been adjusted to pH 7.5 (pH range 6.5 - 8.5) to match the physiologic pH of tears and the product has also been formulated to be iso-osmotic to optimize ocular comfort upon instillation.

Each mL of Sandoz Brinzolamide contains:
Medicinal ingredient: 10 mg brinzolamide (1% w/v).
Preservative: benzalkonium chloride 0.01% w/v.
Non-medicinal ingredients: mannitol, carbomer 974P, tyloxapol, edetate disodium, sodium chloride, hydrochloric acid and/or sodium hydroxide (to adjust pH), and purified water.

Sandoz Brinzolamide is supplied in natural, plastic DROP-TAINER® dispensers with a controlled dispensing-tip containing 5, 10 or 15 mL.

Tamper evidence is provided by a closure with an extended skirt that locks to the bottle finish on application and breaks away from the closure on opening. After cap is removed: if tamper evident snap collar is loos, remove before using product.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

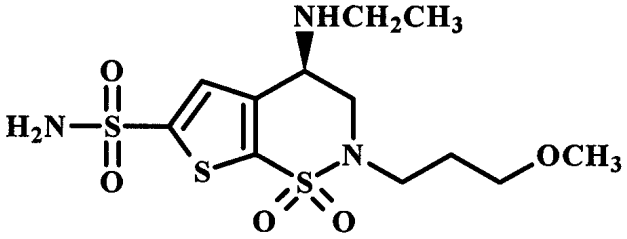
Drug Substance

Proper name: Brinzolamide

Chemical name: (R)-(+)-4-Ethylamino-2-(3-methoxypropyl)-3,4-dihydro-2H-thieno [3,2-e]-1,2-thiazine-6-sulfonamide-1,1-dioxide

Molecular formula and molecular mass: $C_{12}H_{21}N_3O_5S_3$; 383.5

Structural formula:



Physicochemical properties: White powder; Insoluble in water and slightly soluble in methanol and ethanol; melting point of about 131°C

CLINICAL TRIALS

Brinzolamide ophthalmic suspension 1%, dosed two or three times per day (BID or TID) in patients with primary open-angle glaucoma or ocular hypertension, produced significant reductions in intraocular pressure (IOP) when used either as primary therapy or when used adjunctively to timolol maleate ophthalmic solution 0.5% BID.

Monotherapy: When used as primary therapy in two, well-controlled, three-month clinical studies (N = 463 and 572 patients), brinzolamide ophthalmic 1% suspension produced significant reductions in IOP when dosed either BID (3.4 to 5.7 mmHg) or TID (4.1 to 5.6 mmHg). These IOP reductions were statistically equivalent to each other and to the reductions (4.3 to 5.9 mmHg) observed with dorzolamide hydrochloride ophthalmic solution 2% dosed TID in the same studies. From a responder analysis, it was determined that 38 to 75% of patients receiving brinzolamide ophthalmic 1% suspension BID and 48 to 80% of the patients receiving brinzolamide ophthalmic 1% suspension TID as primary therapy achieved either an IOP reduction ≥ 5 mmHg or had their IOP reduced to ≤ 21 mmHg. In comparison, 45 to 80% of the patients receiving dorzolamide hydrochloride ophthalmic 2% TID were determined to have achieved these same reductions.

Ocular comfort: In two, well-controlled, one week studies in patients (N = 109 and 104) with open-angle glaucoma or ocular hypertension, brinzolamide ophthalmic 1% suspension TID was demonstrated to be more comfortable than dorzolamide hydrochloride ophthalmic 2% TID. In these studies, a significantly greater percentage of patients experienced **no discomfort** with brinzolamide ophthalmic 1% suspension (71 to 81%) as compared to dorzolamide hydrochloride ophthalmic 2% (17 to 20%).

Adjunctive therapy to beta-blockers: The IOP-lowering efficacy and safety of brinzolamide ophthalmic 1% suspension TID, dosed adjunctively to timolol (a beta-blocker) has been established in a three month clinical trial in 132 patients who, while using timolol 0.5%, had predose IOP measurement of 24 mmHg to 36 mmHg. When dosed adjunctively to timolol 0.5% BID, brinzolamide ophthalmic 1% suspension provided a small but statistically significant additional reduction in IOP: 3.2 to 4.1 mmHg reduction for the group (with timolol 0.5% BID and brinzolamide ophthalmic 1% TID treatments) versus 1.0 to 2.6 mmHg reduction for the group with timolol 0.5% treatment alone (p-value < 0.05).

Long term: A long-term multicenter clinical trial was conducted in which 379 patients with primary open angle glaucoma or ocular hypertension received brinzolamide BID or TID for at least 12 months. Both BID and TID dosing with brinzolamide produced clinically and statistically significant IOP reductions from baseline (3.2 to 3.9 mm) at each treatment visit. These IOP reductions were statistically equivalent to each other and were maintained for the 12 month treatment period. Adverse events related to therapy demonstrate that brinzolamide 1% dosed BID or TID was safe and well-tolerated. The most frequently reported related ocular adverse events for brinzolamide were transient blurred vision (5.9%) and ocular discomfort (4.3%). There were no clinically relevant changes in hematology, blood chemistry or urinalysis. Brinzolamide 1% BID or TID did not have any negative effect on corneal health as evaluated by specular microscopy of the corneal endothelium.

DETAILED PHARMACOLOGY

Mechanism of Action

Carbonic anhydrase (CA) is an enzyme found in many tissues of the body including the eye. It catalyzes the reversible reaction involving the hydration of carbon dioxide and the dehydration of carbonic acid. In humans, CA exists as a number of isoenzymes, the most active being carbonic anhydrase II (CA-II), found primarily in red blood cells (RBCs), but also in other tissues. Inhibition of CA in the ciliary processes of the eye decreases aqueous humor secretion, presumably by slowing the formation of bicarbonate ions with subsequent reduction in sodium and fluid transport. The result is a reduction in intraocular pressure (IOP).

Brinzolamide 1% ophthalmic suspension contains brinzolamide, a potent inhibitor of CA-II with an *in vitro* IC_{50} of 3.2 nM and a K_i of 0.13 nM against CA-II. Brinzolamide has also been shown to have little or no affinity for 34 known receptors or second messenger systems indicating that it is highly selective for CA-II and should have minimum potential for inducing non-CAI related side-effects. Following topical ocular administration, brinzolamide reduces elevated IOP.

Elevated IOP is a major risk factor in the pathogenesis of optic nerve damage and glaucomatous visual field loss.

Pharmacokinetics/Pharmacodynamics
Following topical ocular administration, brinzolamide is absorbed into the systemic circulation. Due to its high affinity for CA-II, brinzolamide distributes extensively into the RBCs and exhibits a long half-life in whole blood (approximately 111 days). In humans, the metabolite N-desethyl brinzolamide is formed, which also binds to CA and accumulates in RBCs. This metabolite binds mainly to CA-I in the presence of brinzolamide. In plasma, both parent brinzolamide and N-desethyl brinzolamide concentrations are low and generally below assay quantitation limits (<10 ng/mL). Binding to plasma proteins is not extensive (about 60%). Brinzolamide is eliminated predominantly in the urine as unchanged drug. N-Desethyl brinzolamide is also found in the urine along with lower concentrations of the N-desmethoxypropyl and O-desmethyl metabolites.

An oral pharmacokinetic study was conducted in which healthy volunteers received 1 mg capsules of brinzolamide twice per day for up to 32 weeks. This regimen provided a higher rate of systemic drug input than topical ocular administration of brinzolamide ophthalmic suspension 1% dosed to both eyes three times per day, and allowed more rapid saturation of systemic CA-II and achievement of systemic steady state than by topical dosing. RBC CA activity was measured to assess the degree of systemic CA inhibition. Brinzolamide saturation of RBC CA-II was achieved within 4 weeks (RBC concentrations of approximately 20 mcM). N-Desethyl brinzolamide accumulated in RBCs to steady-state within 20-28 weeks reaching concentrations ranging from 6-30 mcM. The inhibition of total RBC CA activity at steady-state was approximately 70-75%, which is below that expected to adversely affect renal function or respiration.

In a topical ocular study, patients with open-angle glaucoma or ocular hypertension received brinzolamide ophthalmic suspension 1% either two or three times per day for up to 18 months. Steady-state concentrations of brinzolamide were reached for most subjects within 6-9 months. Brinzolamide RBC concentrations were similar to those found in the oral study, but levels of the N-desethyl metabolite were lower. Carbonic anhydrase activity was approximately 40-70% of predose levels, indicating a degree of inhibition that was substantially lower than observed orally and unlikely to elicit systemic side effects.

TOXICOLOGY

Acute Toxicity
The oral LD_{50} of brinzolamide in rats was found to be between 1000 to 2000 mg/kg.

Long Term Toxicity
Repeated dose studies in rats and mice have demonstrated brinzolamide to possess a general toxicity profile consistent with those of other carbonic anhydrase inhibitors. In a chronic (six-month) study of brinzolamide administered orally to male and female Fischer 344 rats, renal mineralization was seen in female rats in the mid and high dosage groups of 3 and 8 mg/kg/day

(62 and 166 times the recommended human ophthalmic dose). Minimal to mild nephropathy was observed in females at the highest dosage. Renal and urinary findings were not seen in rats given oral doses equivalent to approximately 20 times the recommended human ophthalmic dose. The increased incidence of renal and urinary findings seen in the mid and high-dose rats is a class-effect of carbonic anhydrase inhibitors in rats. Rats are particularly prone to developing renal pathology in response to foreign bodies, compounds causing crystalluria, and diverse sodium salts.

Carbonic anhydrase activity has been observed in both the cytoplasm and around the plasma membranes of the corneal endothelium. In a twelve month topical ocular primate study, continued administration of with brinzolamide 1% ophthalmic suspension resulted in no significant effect on the corneal endothelium as evaluated by specular microscopy.

Carcinogenicity
Carcinogenicity data on brinzolamide are not available.

Mutagenicity
The following tests for mutagenic potential were negative: (1) *in vivo* mouse micronucleus assay; (2) *in vitro* mammalian forward mutation assay; (3) *in vivo* sister chromatid exchange assay; and (4) Ames *E. coli* test.

Reproduction and Teratology
In reproduction studies of brinzolamide in rats, there were no adverse effects on the fertility or reproductive capacity of males or females at doses up to 18 mg/kg/day (375 times the recommended human ophthalmic dose).

Developmental toxicity studies with brinzolamide in rabbits at oral doses of 1, 3 and 6 mg/kg/day (43, 129 and 258 times the recommended human ophthalmic dose) produced maternal toxicity at 6 mg/kg/day and a significant increase in the number of fetal variations, such as accessory skull bones, which was only slightly higher than the historic value at 1 and 6 mg.kg. In rats, statistically decreased body weights of fetuses from dams receiving oral doses of 18 mg/kg/day during gestation were proportional to the reduced maternal weight gain, with no statistically significant effects on organ or tissue development. Increases in unossified sternebrae, reduced ossification of the skull and unossified hyoid that occurred at 6 and 18 mg/kg were not statistically significant. No treatment-related malformations were seen. Following oral administration of ^{14}C-brinzolamide to pregnant rats, radioactivity was found to cross the placenta and was present in the fetal tissues and blood.

Ocular Administration
No changes in ocular, renal or urinary pathology were seen in rabbits given brinzolamide, up to 4%, dosed topically to the eye QID for six months (88 times the recommended human ophthalmic dose) or monkeys dosed topically to the eye TID at concentrations up to 4% brinzolamide (~66 times the recommended human ophthalmic dose) for one year.

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9. Alcon Canada Inc. Product Monograph: AZOPT™, Control #195439, Date of Preparation: August 26, 2016

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE
PATIENT MEDICATION INFORMATION

[Pr] SANDOZ BRINZOLAMIDE
Brinzolamide Ophthalmic Suspension

Read this carefully before you start taking **Sandoz Brinzolamide** 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 Brinzolamide**.

What is Sandoz Brinzolamide used for?
Sandoz Brinzolamide is used to treat high pressure in the eyes (*ocular hypertension*) in adults with ocular hypertension or open-angle glaucoma. If this high pressure is not reduced, it could eventually damage your eyes.

How does Sandoz Brinzolamide work?
High pressure in the eye(s): Your eyes contain a clear, watery liquid, which feeds the inside of the eye. Liquid is always emptying out of the eye, and more liquid is always being produced. If the liquid fills up faster than it empties, the pressure inside the eye builds up. If the pressure gets too high, it can damage your eyesight.

Sandoz Brinzolamide contains brinzolamide, a carbonic anhydrase inhibitor. It works by reducing the production of liquid in the eyes, which lowers the pressure in the eyes.

What are the ingredients in Sandoz Brinzolamide?
Medicinal ingredients: brinzolamide, 0.1% w/v
Non-medicinal ingredients: benzalkonium chloride as a preservative, carbomer 974P, edetate disodium, mannitol, sodium chloride, tyloxapol, and purified water. Tiny amounts of hydrochloric acid or sodium hydroxide are added to maintain proper pH balance.

Sandoz Brinzolamide comes in the following dosage forms:
Liquid (eye drops) supplied in a 5, 10 and 15 mL plastic bottle

Do not use Sandoz Brinzolamide if you:
- Allergic (*hypersensitive*) to brinzolamide or any of the other ingredients in Sandoz Brinzolamide (see **What are the ingredients in Sandoz Brinzolamide?**).
- Allergic to a group of medicines called sulfonamides (used to treat diabetes and infections).
- Have severe kidney problems.
- Have too much acidity in your blood (a condition called hyperchloremic acidosis).

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Sandoz Brinzolamide. Talk about any health conditions or problems you may have, including if you:
- Have mild to moderate kidney problems.
- Have liver problems.
- Have dry eyes or problems with your cornea.
- Have a type of glaucoma known as acute angle-closure glaucoma.

- Are taking other carbonic anhydrase inhibitors.
- Are pregnant, may be pregnant or planning to become pregnant.
- Are breastfeeding or planning to breast-feed.

Other warnings you should know about:
Sandoz Brinzolamide should not be used by children under 18 years of age.

If you wear contact lenses: Sandoz Brinzolamide contains benzalkonium chloride as a preservative; it may stain soft contact lenses. Do not use Sandoz Brinzolamide while wearing contact lenses. If you wear contact lenses, remove them before applying Sandoz Brinzolamide and wait at least 15 minutes after using the drops before putting your contact lenses back in.

Driving and using machines: You may find your vision is blurred for a short time just after using Sandoz Brinzolamide. Do not drive or use machines until your vision is clear.

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

Drug interaction studies have not been done with Sandoz Brinzolamide.

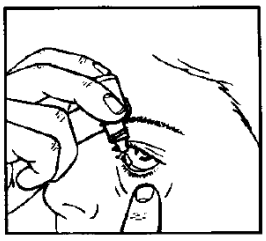
The following may interact with Sandoz Brinzolamide:
- Other carbonic anhydrase inhibitors.
- Antivirals, antifungals and antibiotics, such as ketoconazole, itraconazole, clotrimazole, ritonavir, and troleandomycin.
- Salicylates, such as acetylsalicylic acid.

How to take Sandoz Brinzolamide:
Always use Sandoz Brinzolamide exactly as your doctor has told you.

Usual adult dose:
1 drop in the eye(s) twice a day.

If needed after 4 weeks, dosing can be increased to 1 drop in the eye(s) 3 times a day.

How to use: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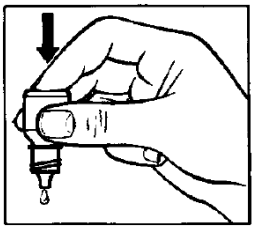
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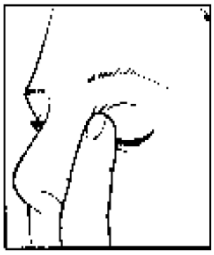
3

- Get the Sandoz Brinzolamide bottle and a mirror (if needed).
- Wash your hands.
- Shake well before use.

- Twist off the cap. If the security snap collar is loose after removing the cap, remove the snap collar before using Sandoz Brinzolamide.
- Hold the bottle, pointing down, between your thumb and fingers.
- Tilt your head back. Pull down your eyelid with a clean finger, until there is a 'pocket' between the eyelid and your eye. The drop will go in here (picture 1).
- Bring the bottle tip close to the eye. Use the mirror if it helps.
- Don't touch your eye or eyelid, surrounding areas or other surfaces with the dropper. It could contaminate the drops, cause an eye infection and damage the eyes.
- Gently press on the base of the bottle to release one drop of Sandoz Brinzolamide at a time (picture 2). Do not squeeze the bottle: it is designed so that a gentle press on the bottom of the bottle is all that it needs.
- After using Sandoz Brinzolamide, press a finger into the corner of your eye, by the nose for 2 minutes (picture 3). This helps to stop Sandoz Brinzolamide from getting into the rest of the body.
- If you miss, wipe up and try again.
- If you take drops in both eyes, repeat the steps for your other eye.
- Close the bottle cap firmly immediately after use.

If you are using other eye drops, wait at least 10 minutes between putting in Sandoz Brinzolamide and the other drops.

Overdose:
If you use more Sandoz Brinzolamide than you should, rinse your eye(s) with warm water. Do not apply any more drops until it is time for your next regular dose.

If you think you have taken too much Sandoz Brinzolamide, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:
If you forget to use Sandoz Brinzolamide, apply a single drop as soon as you remember. If it is close to your next regular dose, skip the missed dose. Do not use a double dose to make up the missed dose.

What are possible side effects from using Sandoz Brinzolamide?
These are not all the possible side effects you may feel when taking Sandoz Brinzolamide.

If you experience any side effects not listed here:
- Talk your healthcare professional.
- See the WARNINGS AND PRECAUTIONS section of this document.

The most common eye side effects are:
- Blurred vision.
- Eye discomfort.
- A feeling that something is in the eye.
- Dry eye.
- Red eyes.
- Eye pain.

- Headache.
- A bad taste in the mouth.

Less common side effects in the eyes include:

- Abnormal or reduced vision.
- Eyelid itching.
- Discharge.
- Fatigue.
- Crusty eyelids.
- Increased tearing.
- Damage to the eye surface (cornea).
- A sticky feeling.
- Allergy.
- Double vision.
- Numbness.
- Swelling.
- Sensitivity to light.
- Flashes of light.

Less common side effects in the rest of the body include:

- Dry mouth.
- Indigestion.
- Nausea.
- Dizziness.
- A tingling sensation.
- Depression.
- Cough.
- Difficulty breathing.
- Sore throat or throat irritation.
- Itchy or runny nose.
- Hair loss.
- Red or itchy skin, skin rash or hives.
- Irregular heart rate.
- Ringing in the ears.
- Upset stomach.
- Diarrhea.
- Lack of energy or feeling tired (fatigue).
- Feeling jittery or irritable.
- Memory loss.
- Sleepiness or inability to sleep.
- Nasal or sinus congestion.

- Dry nose.
- Loss of appetite.
- Joint pain.
- Numbness.
- Decreased blood pressure.

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 Heart disease (angina pectoris): feeling of pain and/or pressure in the chest			✓

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

Reporting Side Effects
You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.
3 ways to report:
- Online at MedEffect;
- By calling 1-866-234-2345 (toll-free);
- By completing a Consumer Side Effect Reporting Form and sending it by:
  - Fax to 1-866-678-6789 (toll-free), or
  - Mail to: Canada Vigilance Program
    Health Canada, Postal Locator 0701E
    Ottawa, ON
    K1A 0K9

  Postage paid labels and the Consumer Side Effect Reporting Form are available at MedEffect.

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:
Store at 4-30°C. Keep bottle tightly closed when not using.

Keep out of reach and sight of children.

If you want more information about Sandoz Brinzolamide:
- 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; the manufacturer's website www.sandoz.ca or by calling 1-800-361-3062.

This leaflet was prepared by Sandoz Canada Inc.

Last Revised: December 02, 2016