BRINZOLAMIDE- brinzolamide suspension/ drops
Bryant Ranch Prepack

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use BRINZOLAMIDE OPHTHALMIC SUSPENSION safely and effectively. See full prescribing information for BRINZOLAMIDE OPHTHALMIC SUSPENSION.

BRINZOLAMIDE ophthalmic suspension 1%
Sterile topical ophthalmic drops
Initial U.S. Approval: 1998

INDICATIONS AND USAGE

Brinzolamide ophthalmic suspension is a carbonic anhydrase inhibitor indicated for in the treatment of elevated intraocular pressure in patients with ocular hypertension or open-angle glaucoma (1).

DOSAGE AND ADMINISTRATION

- Instill one drop in the affected eye(s) three times daily (2).
- If more than one topical ophthalmic drug is being used, the drugs should be administered at least ten (10) minutes apart (2).

DOSAGE FORMS AND STRENGTHS

- Solution containing 10 mg/mL brinzolamide (3)

CONTRAINDICATIONS

- Hypersensitivity to any component of this product (4)

WARNINGS AND PRECAUTIONS

- Sulfonamide hypersensitivity reactions (5.1).
- Corneal edema may occur in patients with low endothelial cell counts (5.2).

ADVERSE REACTIONS

Most common adverse reactions are blurred vision and bitter, sour or unusual taste (6.1).
To report SUSPECTED ADVERSE REACTIONS, contact Sandoz Inc., at 1-800-525-8747 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- There is a potential additive effect of the known systemic effects of carbonic anhydrase inhibition in patients receiving both oral and topical carbonic anhydrase inhibitors (7.1).
- Rare instances of acid-base alterations have occurred with high-dose salicylate therapy (7.2).

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 9/2021

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Brinzolamide ophthalmic suspension 1% is a carbonic anhydrase inhibitor indicated in the treatment of elevated intraocular pressure in patients with ocular hypertension or open-angle glaucoma.

2 DOSAGE AND ADMINISTRATION

The recommended dose is one drop of brinzolamide ophthalmic suspension 1% in the affected eye(s) three times daily. Brinzolamide ophthalmic suspension 1% may be used concomitantly with other topical ophthalmic drug products to lower intraocular

pressure. If more than one topical ophthalmic drug is being used, the drugs should be administered at least ten (10) minutes apart.

3 DOSAGE FORMS AND STRENGTHS

Solution containing 10 mg/mL brinzolamide.

4 CONTRAINDICATIONS

Brinzolamide ophthalmic suspension 1% is contraindicated in patients who are hypersensitive to any component of this product.

5 WARNINGS AND PRECAUTIONS

5.1 Sulfonamide Hypersensitivity Reactions

Brinzolamide ophthalmic suspension 1% is a sulfonamide and although administered topically it is absorbed systemically. Therefore, the same types of adverse reactions that are attributable to sulfonamides may occur with topical administration of brinzolamide ophthalmic suspension 1%. 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 recur when a sulfonamide is re-administered irrespective of the route of administration. If signs of serious reactions or hypersensitivity occur, discontinue the use of this preparation.

5.2 Corneal Endothelium

Carbonic anhydrase activity has been observed in both the cytoplasm and around the plasma membranes of the corneal endothelium. There is an increased potential for developing corneal edema in patients with low endothelial cell counts. Caution should be used when prescribing brinzolamide ophthalmic suspension 1% to this group of patients.

5.3 Severe Renal Impairment

Brinzolamide ophthalmic suspension 1% has not been studied in patients with severe renal impairment (CrCl <30 mL/min). Because brinzolamide ophthalmic suspension 1% and its metabolite are excreted predominantly by the kidney, brinzolamide ophthalmic suspension 1% is not recommended in such patients.

5.4 Acute Angle-Closure Glaucoma

The management of patients with acute angle-closure glaucoma requires therapeutic interventions in addition to ocular hypotensive agents. Brinzolamide ophthalmic suspension 1% has not been studied in patients with acute angle-closure glaucoma.

5.5 Contact Lens Wear

The preservative in brinzolamide ophthalmic suspension 1%, benzalkonium chloride, may be absorbed by soft contact lenses. Contact lenses should be removed during instillation

of brinzolamide ophthalmic suspension 1%, but may be reinserted 15 minutes after instillation.

6 ADVERSE REACTIONS

6.1 Clinical Studies Experience

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to the rates in the clinical studies of another drug and may not reflect the rates observed in practice.

In clinical studies of brinzolamide ophthalmic suspension 1%, the most frequently reported adverse reactions reported in 5 to 10% of patients were blurred vision and bitter, sour or unusual taste. Adverse reactions occurring in 1 to 5% of patients were blepharitis, dermatitis, dry eye, foreign body sensation, headache, hyperemia, ocular discharge, ocular discomfort, ocular keratitis, ocular pain, ocular pruritus and rhinitis.

The following adverse reactions were reported at an incidence below 1%: allergic reactions, alopecia, chest pain, conjunctivitis, diarrhea, diplopia, dizziness, dry mouth, dyspnea, dyspepsia, eye fatigue, hypertonia, keratoconjunctivitis, keratopathy, kidney pain, lid margin crusting or sticky sensation, nausea, pharyngitis, tearing and urticaria.

7 DRUG INTERACTIONS

7.1 Oral Carbonic Anhydrase Inhibitors

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 ophthalmic suspension 1%. The concomitant administration of brinzolamide ophthalmic suspension 1% and oral carbonic anhydrase inhibitors is not recommended.

7.2 High-Dose Salicylate Therapy

Carbonic anhydrase inhibitors may produce acid-base and electrolyte alterations. These alterations were not reported in the clinical trials with brinzolamide. However, in patients treated with oral carbonic anhydrase inhibitors, rare instances of acid-base alterations have occurred with high-dose salicylate therapy. Therefore, the potential for such drug interactions should be considered in patients receiving brinzolamide ophthalmic suspension 1%.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

Developmental toxicity studies with brinzolamide in rabbits at oral doses of 1, 3, and 6 mg/kg/day (20, 62, and 125 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 (375 times the recommended human ophthalmic dose) 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.

There are no adequate and well-controlled studies in pregnant women. Brinzolamide ophthalmic suspension 1% should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

8.3 Nursing Mothers

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) were seen during lactation. No other effects were observed. However, following oral administration of ^{14}C-brinzolamide to lactating rats, radioactivity was found in milk at concentrations below those in the blood and plasma.

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from brinzolamide ophthalmic suspension 1%, 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.

8.4 Pediatric Use

A three-month controlled clinical study was conducted in which brinzolamide ophthalmic suspension 1% was dosed only twice a day in pediatric patients 4 weeks to 5 years of age. Patients were not required to discontinue their IOP-lowering medication(s) until initiation of monotherapy with brinzolamide ophthalmic suspension 1%. IOP-lowering efficacy was not demonstrated in this study in which the mean decrease in elevated IOP was between 0 and 2 mmHg. Five out of 32 patients demonstrated an increase in corneal diameter of one millimeter.

8.5 Geriatric Use

No overall differences in safety or effectiveness have been observed between elderly and younger patients.

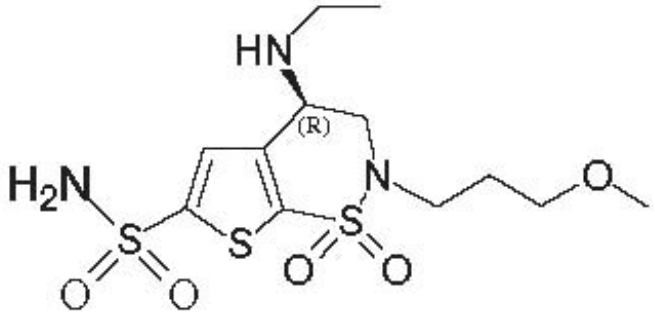
10 OVERDOSAGE

Although no human data are available, electrolyte imbalance, development of an acidotic state, and possible nervous system effects may occur following oral administration of an overdose. Serum electrolyte levels (particularly potassium) and blood pH levels should be monitored.

11 DESCRIPTION

Brinzolamide ophthalmic suspension 1% contains a carbonic anhydrase inhibitor

formulated for multidose topical ophthalmic use. Brinzolamide is described chemically as: (R)-(+)-4-Ethylamino-2-(3-methoxypropyl)-3,4-dihydro-2H-thieno [3,2-e]-1,2-thiazine-6-sulfonamide-1,1- dioxide. Its empirical formula is $C_{12}H_{21}N_3O_5S_3$, and its structural formula is:



Brinzolamide has a molecular weight of 383.5 and a melting point of about 131°C. It is a white powder, which is insoluble in water, very soluble in methanol and soluble in ethanol.

Brinzolamide ophthalmic suspension 1% is supplied as a sterile, aqueous suspension of brinzolamide which has been formulated to be readily suspended and slow settling, following shaking. It has a pH of approximately 7.5 and an osmolality of 300 mOsm/kg.

Each mL of brinzolamide ophthalmic suspension 1% contains:

Active ingredient: brinzolamide 10 mg.

Preservative: Benzalkonium chloride 0.1 mg.

Inactives: mannitol, carbomer 974P, tyloxapol, edetate disodium, sodium chloride, purified water, with hydrochloric acid and/or sodium hydroxide to adjust pH.

12 CLINICAL PHARMACOLOGY

12.1 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, carbonic anhydrase 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 carbonic anhydrase 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 ophthalmic suspension 1% contains brinzolamide, an inhibitor of carbonic anhydrase II (CA-II). Following topical ocular administration, brinzolamide inhibits aqueous humor formation and reduces elevated intraocular pressure. Elevated intraocular pressure is a major risk factor in the pathogenesis of optic nerve damage and glaucomatous visual field loss.

12.3 Pharmacokinetics

Following topical ocular administration, brinzolamide is absorbed into the systemic circulation. Due to its 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 approximately 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 approximates the amount of drug delivered by topical ocular administration of brinzolamide ophthalmic suspension 1% dosed to both eyes three times per day and simulates systemic drug and metabolite concentrations similar to those achieved with long-term 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 to 28 weeks reaching concentrations ranging from 6 to 30 mcM. The inhibition of CA-II activity at steady-state was approximately 70 to 75%, which is below the degree of inhibition expected to have a pharmacological effect on renal function or respiration in healthy subjects.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Brinzolamide caused urinary bladder tumors in female mice at oral doses of 10 mg/kg/day and in male rats at oral doses of 8 mg/kg/day in 2 year studies. Brinzolamide was not carcinogenic in male mice or female rats dosed orally for up to 2 years. The carcinogenicity appears secondary to kidney and urinary bladder toxicity. These levels of exposure cannot be achieved with topical ophthalmic dosing in humans. The following tests for mutagenic potential were negative: (1) *in vivo* mouse micronucleus assay; (2) *in vivo* sister chromatid exchange assay; and (3) Ames *E. coli* test. The *in vitro* mouse lymphoma forward mutation assay was negative in the absence of activation, but positive in the presence of microsomal activation. 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).

14 CLINICAL STUDIES

In two, three-month clinical studies, brinzolamide ophthalmic suspension 1% dosed three times per day in patients with elevated intraocular pressure (IOP), produced significant reductions in IOPs (4 to 5 mmHg). These IOP reductions are equivalent to the reductions observed with TRUSOPT* (dorzolamide hydrochloride ophthalmic solution) 2% dosed three times per day in the same studies.

In two clinical studies in patients with elevated intraocular pressure, brinzolamide ophthalmic suspension 1% was associated with less stinging and burning upon instillation than TRUSOPT* 2%.

16 HOW SUPPLIED/STORAGE AND HANDLING

Brinzolamide ophthalmic suspension 1% is supplied in plastic DROP-TAINER® dispensers with a controlled dispensing-tip as follows:

10 mL NDC: 63629-8793-1

Storage and Handling

Store brinzolamide ophthalmic suspension 1% at 4°C to 30°C (39°F to 86°F). Shake well before use.

DROP-TAINER® is registered trademark of Alcon Research, Ltd.

17 PATIENT COUNSELING INFORMATION

17.1 Sulfonamide Reactions

Advise patients that if serious or unusual ocular or systemic reactions or signs of hypersensitivity occur, they should discontinue the use of the product and consult their physician.

17.2 Temporary Blurred Vision

Vision may be temporarily blurred following dosing with brinzolamide ophthalmic suspension 1%. Advise patients to exercise care in operating machinery or driving a motor vehicle.

17.3 Avoiding Contamination of the Product

Instruct patients to avoid allowing the tip of the dispensing container to contact the eye or surrounding structures or other surfaces, since the product can become contaminated by common bacteria known to cause ocular infections. Serious damage to the eye and subsequent loss of vision may result from using contaminated solutions.

17.4 Intercurrent Ocular Conditions

Advise patients that if they have ocular surgery or develop an intercurrent ocular condition (e.g., trauma or infection), they should immediately seek their physician's advice concerning the continued use of the present multidose container.

17.5 Concomitant Topical Ocular Therapy

If more than one topical ophthalmic drug is being used, the drugs should be administered at least ten minutes apart.

17.6 Contact Lens Wear

The preservative in brinzolamide ophthalmic suspension 1%, benzalkonium chloride, may

be absorbed by soft contact lenses. Contact lenses should be removed during instillation of brinzolamide ophthalmic suspension 1%, but may be reinserted 15 minutes after instillation.

*TRUSOPT is a registered trademark of Merck & Co., Inc.

Manufactured by

Alcon Laboratories, Inc.

Fort Worth, Texas 76134 for

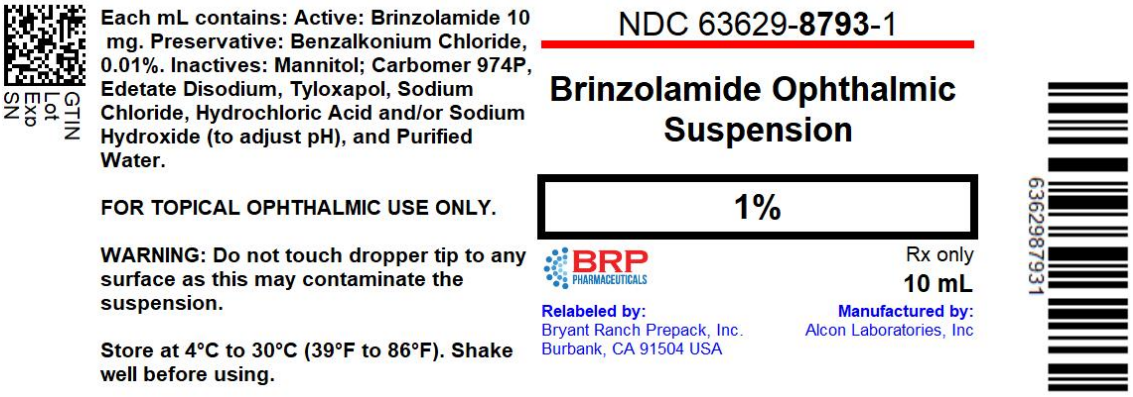
Sandoz Inc.

Princeton, NJ 08540

T2017-74

November 2015

Brinzolamide Ophthalmic Susp 1% #10



BRINZOLAMIDE

brinzolamide suspension/ drops

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:63629-8793(NDC:0781-6014)
Route of Administration	OPHTHALMIC		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
BRINZOLAMIDE (UNII: 9451Z89515) (BRINZOLAMIDE - UNII:9451Z89515)	BRINZOLAMIDE	10 mg in 1 mL

Inactive Ingredients

Ingredient Name	Strength
MANNITOL (UNII: 3OWL53L36A)	
TYLOXAPOL (UNII: Y27PUL9H56)	
EDETATE DISODIUM (UNII: 7FLD91C86K)	
SODIUM CHLORIDE (UNII: 451W47IQ8X)	
HYDROCHLORIC ACID (UNII: QTT17582CB)	
SODIUM HYDROXIDE (UNII: 55X04QC32I)	
WATER (UNII: 059QF0KO0R)	
BENZALKONIUM CHLORIDE (UNII: F5UM2KM3W7)	
CARBOMER HOMOPOLYMER TYPE C (ALLYL PENTAERYTHRITOL CROSSLINKED) (UNII: 4Q93RCW27E)	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:63629-8793-1	1 in 1 CARTON	09/09/2021	
1		10 mL in 1 BOTTLE, PLASTIC; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA authorized generic	NDA020816	03/08/2021	

Labeler - Bryant Ranch Prepack (171714327)

Registrant - Bryant Ranch Prepack (171714327)

Establishment

Name	Address	ID/FEI	Business Operations
Bryant Ranch Prepack		171714327	REPACK(63629-8793) , RELABEL(63629-8793)

Revised: 1/2024 Bryant Ranch Prepack