

PRODUCT MONOGRAPH

AZOPT™

(Brinzolamide Ophthalmic Suspension)

1%

THERAPEUTIC CLASSIFICATION:

Elevated Intraocular Pressure Therapy

(Topical Carbonic Anhydrase Inhibitor)

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THERAPEUTIC CLASSIFICATION:

Elevated Intraocular Pressure Therapy

(Topical Carbonic Anhydrase Inhibitor)

ACTIONS & CLINICAL PHARMACOLOGY

AZOPT (Brinzolamide 1%) Ophthalmic Suspension 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, carbonic anhydrase exists as a number of isoenzymes, the most active being carbonic anhydrase II (CA-II), found primarily in red blood cells (RBC's), 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).

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 trace concentrations (<1% of the dose) of the N-desmethoxypropyl and O-desmethyl metabolites.

INDICATIONS AND CLINICAL USE

AZOPT™ (Brinzolamide 1%) Ophthalmic Suspension is indicated in the treatment of elevated intraocular pressure in patients with ocular hypertension or open-angle glaucoma.

CONTRAINDICATIONS

AZOPT™ (Brinzolamide 1%) Ophthalmic Suspension is contraindicated in patients who are hypersensitive to any component of this product.

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

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 AZOPT™ suspension. The concomitant administration of AZOPT™ and oral carbonic anhydrase inhibitors is not recommended.

WARNINGS

AZOPT™ (Brinzolamide 1%) Ophthalmic Suspension 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 AZOPT™. 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 readministered irrespective of the route of administration. If signs of serious reactions or hypersensitivity occur, discontinue the use of this preparation.

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

AZOPT™ suspension has not been studied in patients with hepatic impairment and should therefore be used with caution in such patients.

The preservative in AZOPT™ Ophthalmic Suspension, benzalkonium chloride, may be absorbed by soft contact lenses. Contact lenses should be removed during instillation of AZOPT™ but may be reinserted 15 minutes after instillation.

Pediatric Use:

Safety and effectiveness in pediatric patients have not been established.

Use During Pregnancy:

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

Nursing Mothers:

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 AZOPT™ suspension, 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.

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 ¹⁴C-brinzolamide to lactating rats, radioactivity was found in milk at concentrations below those in the blood and plasma.

PRECAUTIONS

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 AZOPT™ (Brinzolamide 1%) Ophthalmic Suspension resulted in no significant effect on the corneal endothelium as evaluated by specular microscopy.

Patients should be instructed to avoid allowing the tip of the dispensing container to contact the eye or surrounding structures or with other surfaces.

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

Effects on Ability to Drive and to Use Machines

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

Drug Interactions:

Although acid-base and electrolyte alterations were not reported in the clinical trials with brinzolamide, these changes have been reported with oral carbonic anhydrase inhibitors and have, in some instances, resulted in drug interactions (e.g., toxicity associated with high-dose salicylate therapy). Therefore, the potential for such drug interactions should be considered in patients receiving AZOPT™ suspension.

Geriatric Use:

In well-controlled clinical studies of AZOPT™ 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:

In well-controlled clinical studies of AZOPT™ (Brinzolamide 1%) Ophthalmic Suspension, adverse reactions related to AZOPT™ were generally mild to moderate and usually did not lead to discontinuation of therapy. The following table lists for AZOPT™ 1% and Placebo reported adverse events possibly, probably or definitely related to therapy occurring at an incidence of 1% or greater.

	AZOPT™ 1% N=1173	Placebo N=101
Ocular	Percent Incidence	Percent Incidence
Blurred Vision	5.0	2.0
Discomfort	2.6	3.0
Foreign Body Sensation	1.8	0
Dry Eye	1.2	1.0
Hyperemia	1.1	1.0
Pain	1.0	1.0
Nonocular		
<u>Body As A Whole</u> Headache	1.5	1.0
<u>Special Senses</u> Taste Perversion	5.6	1.0

The following ocular-related adverse reactions to AZOPT™ 1% suspension were reported at an incidence below 1% - pruritus, discharge, keratitis, blepharitis, tearing, conjunctivitis, lid margin crusting, sticky sensation, abnormal vision, and eye fatigue.

The following non-ocular related adverse reactions to AZOPT™ 1% suspension were reported at an incidence below 1%: dry mouth, nausea, dyspepsia, depression, dizziness, paresthesia, rhinitis, pharyngitis, bronchitis, dyspnea, dermatitis, and alopecia.

SYMPTOMS & TREATMENT OF OVERDOSAGE

Although no human data are available, 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. The oral LD₅₀ of brinzolamide in rats was found to be between 1000 to 2000 mg/kg.

Treatment should be symptomatic and supportive.

DOSAGE AND ADMINISTRATION

Shake well before use.

When used as a monotherapy, the recommended starting dose is 1 drop of AZOPT™ (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.

AZOPT™ suspension may be used as adjunctive therapy with ophthalmic beta-blockers. See information under Clinical Studies.

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

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

Structural Formula:



Molecular Formula:

Molecular Weight:

Description:

Brinzolamide

Solubility: Insoluble in water and slightly soluble in methanol and ethanol

Melting Point: About 131 °C

Composition: AZOPT™ 1% 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 AZOPT™ 1% contains 10 mg brinzolamide. Inactive ingredients are mannitol, carbomer 974P, tyloxapol, edetate disodium, sodium chloride, hydrochloric acid and/or sodium hydroxide (to adjust pH), and purified water. Benzalkonium chloride 0.01% is added as a preservative.

Stability and Storage Recommendations:

Store AZOPT™ Ophthalmic Suspension 1% at 4-30 °C (36-86 °F).

Shake well before use.

AVAILABILITY OF DOSAGE FORMS

Pr AZOPT™ Ophthalmic Suspension 1% is supplied in natural, plastic DROP-TAINER® dispensers with a controlled dispensing-tip containing 5, 10 or 15 mL.

INFORMATION FOR PATIENTS

AZOPT™ (Brinzolamide 1%) Ophthalmic Suspension is a sulfonamide and although administered topically it is absorbed systemically; therefore, the same types of adverse reactions attributable to sulfonamides may occur with topical administration. Patients should be advised 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.

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

Avoid allowing the tip of the dispensing container to contact the eye or surrounding structures or with other surfaces.

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

Contact lenses should be removed before dosing. Reinsertion of lenses may occur 15 minutes after dosing.

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, carbonic anhydrase exists as a number of isoenzymes, the most active being carbonic anhydrase II (CA-II), found primarily in red blood cells (RBC's), 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).

AZOPT™ 1% ophthalmic suspension contains brinzolamide, a potent inhibitor of carbonic anhydrase II (CA-II) with an *in vitro* IC₅₀ 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 intraocular pressure. Elevated intraocular pressure 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 AZOPT™ (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 µM). N-Desethyl brinzolamide accumulated in RBCs to steady-state within 20-28 weeks reaching concentrations ranging from 6-30 µM. 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 AZOPT™ (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.

Clinical Studies:

AZOPT™ (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 TIMOPTIC® 0.5% BID (Timolol Maleate Ophthalmic Solution).

When used as primary therapy in two, well-controlled, three-month clinical studies (N = 463 and 572 patients), AZOPT™ 1% suspension produced significant reductions in intraocular pressure 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 TRUSOPT® (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 AZOPT™ 1% suspension BID and 48 to 80% of the patients receiving AZOPT™ 1% suspension TID as primary therapy achieved either an IOP reduction \geq 5 mmHg or had their IOP reduced to \leq 21 mmHg. In comparison, 45 to 80% of the patients receiving TRUSOPT® 2% TID were determined to have achieved these same reductions.

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

The IOP-lowering efficacy and safety of AZOPT™ 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, AZOPT™ 1% suspension provided a small but statistically significant additional reduction in intraocular pressure: 3.2 to 4.1 mmHg reduction for the group (with timolol 0.5% BID and AZOPT™ 1% TID treatments) versus 1.0 to 2.6 mmHg reduction for the group with timolol 0.5% treatment alone (p-value < 0.05).

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 3.9mm) 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.

TOXICOLOGY

Acute Toxicity

The oral LD₅₀ 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.

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 up to 6 mg/kg/day (125 times the recommended human ophthalmic dose) revealed no effect on fetal development despite significant maternal toxicity. 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. No treatment-related malformations were seen. Following oral administration of ¹⁴C-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 q.i.d. for six months (88 times the recommended human ophthalmic dose) or monkeys dosed topically to the eye t.i.d. at concentrations up to 4% brinzolamide (~66 times the recommended human ophthalmic dose) for one year.

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