HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use AZOPT® safely and effectively. See full prescribing information for AZOPT®.

AZOPT® (brinzolamide ophthalmic suspension) 1% Sterile topical ophthalmic drops

Initial U.S. Approval: 1998

---INDICATIONS AND USAGE---

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

---DOSEAGE AND ADMINISTRATION---

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

---DOSEAGE FORMS AND STRENGTHS---

Solution containing 10 mg/mL brinzolamide (3)

---CONTRAINDICATIONS---

• Hypersensitivity to any component of this product (4)

---WARNINGS AND PRECAUTIONS---

• Cataract: Hypermetropia and hyperopic shift in the refractive error have been reported with topical carbonic anhydrase inhibitors.

---ADVERSE REACTIONS---

Most common adverse reactions are blurred vision and bitter, sour or unusual taste (6).

To report SUSPECTED ADVERSE REACTIONS, contact Alcon Laboratories, Inc. at 1-800-797-9195 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 inhibitors in patients receiving both oral and topical carbonic anhydrase inhibitors (7).

Rare instances of acid-base alterations have occurred with high-dose salicylate therapy (7).

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 11/2015

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---INDICATIONS AND USAGE---

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

---DOSEAGE AND ADMINISTRATION---

The recommended dose is one drop of AZOPT® (brinzolamide ophthalmic suspension) 1% in the affected eye(s) three times daily.

AZOPT® (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.

---DOSEAGE FORMS AND STRENGTHS---

Solution containing 10 mg/mL brinzolamide.

---CONTRAINDICATIONS---

Contraindicated in patients who are hypersensitive to any component of this product.

---WARNINGS AND PRECAUTIONS---

Sulfonamide Hyperчувствительность Reactions

AZOPT® (brinzolamide ophthalmic suspension) 1% is a sulfonamide, and although administered topically is not absorbed systemically. Therefore, the types of adverse reactions that are attributable to sulfonamides may occur with topical administration of AZOPT® (brinzolamide ophthalmic suspension) 1%. Fatalities have occurred, although rarely, due to severe reactions to sulfonamides including Stevens-Johnson syndrome, toxic epidermal necrolysis, lichenoid keratitis, agranulocytosis, aplastic anemia, and other blood dyscrasias. Sulfonamides may also be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

---ADVERSE REACTIONS---

The following adverse reactions were reported at an incidence below 1%: allergic reactions, alopecia, chest pain, conjunctivitis, diarrhea, dyspepsia, dry mouth, dysuria, dyspnea, edema, eosinophilia, fever, fatigue, hypotension, keratoconjunctivitis, keratopathy, kidney pain, lid margin crusting or sticky sensation, nausea, paresthesia, tearing, and urticaria.

---DRUG INTERACTIONS---

Oral Carbonic Anhydrase Inhibitors

Toric brinzolamide antagonizes the effects of carbonic anhydrase inhibition in patients receiving oral carbonic anhydrase inhibitor and AZOPT® (brinzolamide ophthalmic suspension) 1%. The concomitant administration of AZOPT® (brinzolamide ophthalmic suspension) 1% and oral carbonic anhydrase inhibitors is not recommended.

---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 alterations, 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 (312 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 skull were also noted.

---CLINICAL PHARMACOLOGY---

9.1 Pharmacokinetics

Increased intraocular pressure (IOP) results from the increased reabsorption of sodium and fluid into the aqueous humor, resulting in a decrease in the production of aqueous humor. Aqueous humor is balanced by the secretion of bicarbonate ions with subsequent reduction in sodium and fluid. Carbonic anhydrase (CA) is an enzyme found in many tissues of the body and is involved in the process of carbon dioxide transport. The result is a reduction in intraocular pressure (IOP).

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 AZOPT® (brinzolamide ophthalmic suspension) 1%.

---HOW SUPPLIED/STORAGE AND HANDLING---

AZOPT® (brinzolamide ophthalmic suspension) 1% is supplied as a multidose topical ophthalmic form (15 mL NDC 0065-0275-15) as a clear, colorless solution containing 10 mg/mL brinzolamide.

AZOPT® is supplied in a multidose container. Each container is designed to deliver the exact amount of drug, and the container should not be used after the date marked on the container.

---DESCRIPTION---

AZOPT® (brinzolamide ophthalmic suspension) 1% is a carbonic anhydrase inhibitor formulated for multidose topical ophthalmic use. Brinzolamide is described chemically as:

C15H19N5O4S2 • 2H2O

AZOPT® (brinzolamide ophthalmic suspension) 1% is supplied in the form of a sterile ophthalmic solution containing 10 mg/mL brinzolamide hydrochloride, 0.3% hydroxypropyl methylcellulose, 0.5% sodium chloride, and 0.06% sodium benzoate in a slightly buffered solution at 4 to 30°C (39 to 86°F). Shake well before use.

---CLINICAL STUDIES---

A three-month controlled clinical study was conducted in which AZOPT® (brinzolamide ophthalmic suspension) 1% was dosed only once per day in patients with ocular hypertension. IOP-lowering efficacy was not demonstrated in this study in which the mean decrease in IOP at 24 hours was 2.6 mm Hg.

---HOW SUPPLIED/STORAGE AND HANDLING---

AZOPT® (brinzolamide ophthalmic suspension) 1% is supplied in 15 mL containers with a multidose dispenser. The container is designed to deliver the exact amount of drug, and the container should not be used after the date marked on the container. If the solution contains a preservative, it may be used for up to 30 days after opening.

---CONTRAINDICATIONS---

Contraindicated in patients who are hypersensitive to any component of this product.
8.4 Pediatric Use
A three-month controlled clinical study was conducted in which AZOPT® (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 AZOPT®. IOP-lowering efficacy was not demonstrated in this study in which the mean decrease in 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
AZOPT® (brinzolamide ophthalmic suspension) 1% contains a carbonic anhydrase inhibitor formulated for multidose topical ophthalmic use. Brinzolamide is described chemically as: (RS)-(+)-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_{14}H_{17}N_{5}O_{5}S, 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.

AZOPT® (brinzolamide ophthalmic suspension) 1% is supplied as a sterile, aqueous suspension of brinzolamide which has been formulated to be ready for suspension and slow settling, following shaking. It has a pH of approximately 7.3 and an osmolality of 300 mOsm/kg.

Each mL of AZOPT® (brinzolamide ophthalmic suspension) 1% contains: Active ingredient: Brinzolamide 10 mg. Preservatives: Benzalkonium chloride 0.1 mg. Inactives: mannitol, carborner 940, polyethylene glycol, 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 human aqueous humor, a balance exists as a number of sequences, 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).

AZOPT® (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.

12.2 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 exerts 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 mainly contributes to CA-II 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-desmethyln 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 AZOPT® (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 20 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 nasal 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 only for up to 3 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 micromanipulation.