

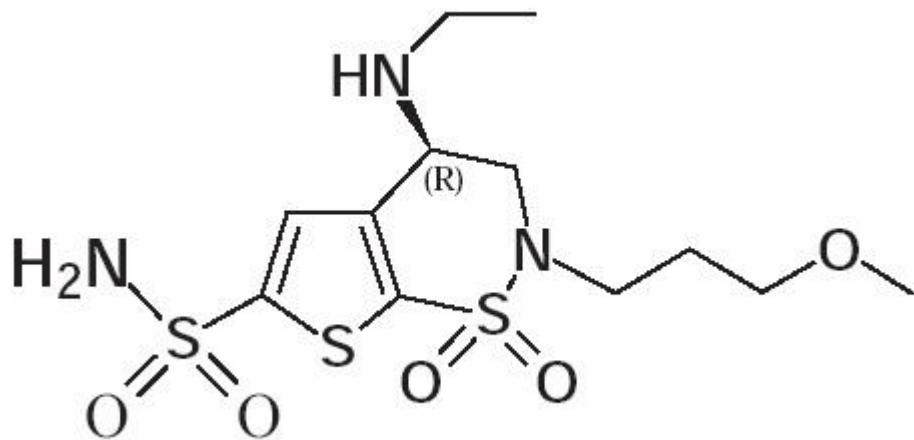
NDA 20-816/S-009

Page 3

Azopt®
(brinzolamide ophthalmic
suspension) 1%

DESCRIPTION

AZOPT® (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 C₁₂H₂₁N₃O₅S₃, 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 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 AZOPT® (brinzolamide ophthalmic suspension) 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.

CLINICAL PHARMACOLOGY

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).

NDA 20-816/S-009

Page 4

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.

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 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 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 µM). N-Desethyl brinzolamide accumulated in RBCs to steady-state within 20-28 weeks reaching concentrations of 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 CA-II activity at steady-state was approximately 70-75%, which is below the degree of inhibition expected to have a pharmacological effect on renal function or respiration in healthy subjects.

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

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

INDICATIONS AND USAGE

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

CONTRAINDICATIONS

AZOPT® (brinzolamide ophthalmic suspension) 1% is contraindicated in patients who are hypersensitive to any component of this product.

NDA 20-816/S-009

Page 5

WARNINGS

AZOPT® (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 AZOPT® (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.

PRECAUTIONS

General

Carbonic anhydrase activity has been observed in both the cytoplasm and around the plasma membranes of the corneal endothelium. The effect of continued administration of AZOPT® (brinzolamide ophthalmic suspension) 1% on the corneal endothelium has not been fully evaluated.

The management of patients with acute angle-closure glaucoma requires therapeutic interventions in addition to ocular hypotensive agents. AZOPT® (brinzolamide ophthalmic suspension) 1% has not been studied in patients with acute angle-closure glaucoma. AZOPT® (brinzolamide ophthalmic suspension) 1% has not been studied in patients with severe renal impairment ($\text{CrCl} < 30 \text{ mL/min}$). Because AZOPT® (brinzolamide ophthalmic suspension) 1% and its metabolite are excreted predominantly by the kidney, AZOPT® (brinzolamide ophthalmic suspension) 1% is not recommended in such patients. AZOPT® (brinzolamide ophthalmic suspension) 1% has not been studied in patients with hepatic impairment and should be used with caution 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® (brinzolamide ophthalmic suspension) 1%. The concomitant administration of AZOPT® (brinzolamide ophthalmic suspension) 1% and oral carbonic anhydrase inhibitor is not recommended.

Information For Patients

AZOPT® (brinzolamide ophthalmic suspension) 1% 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 (see **WARNINGS**).

Vision may be temporarily blurred following dosing with AZOPT® (brinzolamide ophthalmic suspension) 1%. Care should be exercised in operating machinery or driving a motor vehicle.

Patient should be instructed 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.

NDA 20-816/S-009

Page 6

Patient should also be advised 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.

If more than one topical ophthalmic drug is being used, the drugs should be administered at least ten minutes apart. The preservative in AZOPT® (brinzolamide ophthalmic suspension) 1%, benzalkonium chloride, may be absorbed by soft contact lenses. Contact lenses should be removed during instillation of AZOPT® (brinzolamide ophthalmic suspension) 1%, but may be reinserted 15 minutes after instillation.

Drug Interactions

AZOPT® (brinzolamide ophthalmic suspension) 1% contains a carbonic anhydrase inhibitor. Acid-base and electrolyte alterations were not reported in the clinical trials with brinzolamide. However, in patients treated with oral carbonic anhydrase inhibitors, rare instances to drug interactions 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%.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity data on brinzolamide are not available. 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).

Pregnancy

Teratogenic Effects

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 ¹⁴C-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. AZOPT® (brinzolamide ophthalmic suspension) 1% should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

NDA 20-816/S-009
Page 7

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 ¹⁴C-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 AZOPT® (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.

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 elevated IOP was between 0 and 2 mmHg. Five out of 32 patients demonstrated an increase in corneal diameter of one millimeter.

Geriatric Use

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

ADVERSE REACTIONS

In clinical studies of AZOPT® (brinzolamide ophthalmic suspension) 1%, the most frequently reported adverse events associated with AZOPT® (brinzolamide ophthalmic suspension) 1% were blurred vision and bitter, sour or unusual taste. These events occurred in approximately 5-10% of patients. Blepharitis, dermatitis, dry eye, foreign body sensation, headache, hyperemia, ocular discharge, ocular discomfort, ocular keratitis, ocular pain, ocular pruritus and rhinitis were reported at an incidence of 1-5%.

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

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.

NDA 20-816/S-009

Page 8

DOSAGE AND ADMINISTRATION

Shake well before use. The recommended dose is 1 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 minutes apart.

HOW SUPPLIED

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

2.5 mL NDC 0065-0275-24

5 mL NDC 0065-0275-05

10 mL NDC 0065-0275-10

15 mL NDC 0065-0275-15

Storage:Store AZOPT® (brinzolamide ophthalmic suspension) 1% at 4-30°C (39-86°F).

Rx Only

U.S. Patent Nos.: 5,240,923; 5,378,703; 5,461,081; 6,071,904.

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

ALCON

ALCON LABORATORIES, INC.

Fort Worth, Texas 76134 USA

2000-2006 Alcon, Inc.