PRODUCT MONOGRAPH

AZOPT®
Brinzolamide Ophthalmic Suspension
1% w/v

THERAPEUTIC CLASSIFICATION:
Elevated Intraocular Pressure Therapy
(Topical Carbonic Anhydrase Inhibitor)

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PRODUCT MONOGRAPH

AZOPT®
Brinzolamide Ophthalmic Suspension

ACTION & CLINICAL PHARMACOLOGY

AZOPT® 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.

INDICATIONS AND CLINICAL USE

AZOPT® is indicated in the treatment of elevated intraocular pressure (IOP) in adult patients with ocular hypertension or open-angle glaucoma.

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

CONTRAINDICATIONS

AZOPT® is contraindicated in patients with:
- Hypersensitivity to brinzolamide or to any ingredient in the formulation or component of the container (see Composition, Availability of Dosage Form).
- Hypersensitivity to sulfonamides.
- Severe renal impairment.
Hyperchloremic acidosis.

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

The concomitant administration of AZOPT* 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 AZOPT*, is absorbed systematically.

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

AZOPT* contains brinzolamide, a sulfonamide. The same types of adverse reactions that are attributable to sulfonamides may occur with topical administration of AZOPT*. Hypersensitivity reactions common to all sulfonamide derivatives can occur in patients receiving 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 re-administered irrespective of the route of administration. If signs of serious reactions or hypersensitivity occur, discontinue the use of AZOPT*.

Acid-base disturbances have been reported with oral carbonic anhydrase inhibitors. Caution is advised when using AZOPT* in patients with mild to moderate renal impairment because of the possible risk of metabolic acidosis. AZOPT* 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 AZOPT*. The concomitant administration of AZOPT* 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. AZOPT* is not recommended for use in patients with acute angle-closure glaucoma due to a lack of studies in such patients.
**Hepatic**
AZOPT® 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 AZOPT® is absorbed systematically, caution is advised when using AZOPT® 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.

AZOPT® contains the preservative benzalkonium chloride, which may cause eye irritation and is known to discolor soft contact lenses. Contact with soft contact lenses is to be avoided. Patients must be instructed to remove contact lenses prior to instillation of AZOPT® 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.

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

**Renal**
AZOPT® is contraindicated in patients with severe renal impairment. Caution is advised when using AZOPT® in patients with mild to moderate renal impairment.

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

**Special Populations**
**Pregnant Women:**
AZOPT® 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:
AZOPT® should not be used by women nursing neonates/infants.

It is not known whether topical AZOPT® 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 14C-brinzolamide to lactating rats, radioactivity was found in milk at concentrations below those in the blood and plasma.

Geriatrics (> 65 years of age):
In well-controlled clinical studies of AZOPT®, 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.

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

**DRUG INTERACTIONS**

No specific drug interaction studies have been performed with AZOPT®.

AZOPT® 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 AZOPT®.

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 AZOPT® is not recommended. AZOPT® 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 AZOPT® 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.
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 with AZOPT®, adverse reactions related to AZOPT® 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%)

<table>
<thead>
<tr>
<th>MedDRA Preferred Term (v15.1)</th>
<th>AZOPT® 1% N=1173 (%)</th>
<th>Placebo N=101 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Eye disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vision blurred</td>
<td>5.0</td>
<td>2.0</td>
</tr>
<tr>
<td>Ocular discomfort</td>
<td>2.6</td>
<td>3.0</td>
</tr>
<tr>
<td>Foreign body sensation in eyes</td>
<td>1.8</td>
<td>0</td>
</tr>
<tr>
<td>Dry Eye</td>
<td>1.2</td>
<td>1.0</td>
</tr>
<tr>
<td>Ocular hyperemia</td>
<td>1.1</td>
<td>1.0</td>
</tr>
<tr>
<td>Eye pain</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td><strong>Nervous system disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>1.5</td>
<td>1.0</td>
</tr>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>5.6</td>
<td>1.0</td>
</tr>
</tbody>
</table>

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.

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**SYMPTOMS & TREATMENT OF OVERDOSAGE**

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

If overdose with AZOPT® 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.

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**DOSAGE AND ADMINISTRATION**

**Recommended Dose**

**Monotherapy:**

When used as a monotherapy, the recommended starting adult dose is 1 drop of AZOPT® 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:**

AZOPT® may be used as adjunctive therapy with ophthalmic beta-blockers (see PHARMACOLOGY, Clinical Studies).

When AZOPT® 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.
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:**

![Structural Formula Image]

**Molecular Formula:** C_{12}H_{21}N_{3}O_{5}S_{3}
**Molecular Weight:** 383.5
**Description:** White powder
**Solubility:** Insoluble in water and slightly soluble in methanol and ethanol
**Melting Point:** About 131°C

**Composition:**
AZOPT® 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® 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.

**Stability and Storage Recommendations:**
Store AZOPT® at 4-30°C (36-86°F). Keep bottle tightly closed when not in use. Keep out of the reach and sight of children.

**AVAILABILITY OF DOSAGE FORMS**
AZOPT® 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 loose, remove before using product.

**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).

AZOPT* 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 AZOPT* 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 6-30μM. 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* 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 pre-dose levels, indicating a degree of inhibition that was substantially lower than observed orally and unlikely to elicit systemic side effects.

**Clinical Studies:**
AZOPT®, 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).

**Monotherapy:** When used as primary therapy in two, well-controlled, three-month clinical studies (N = 463 and 572 patients), AZOPT® 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 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® BID and 48 to 80% of the patients receiving AZOPT® 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 TRUSOPT® 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, AZOPT® 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® (71 to 81%) as compared to TRUSOPT® 2% (17 to 20%).

**Adjunctive therapy to beta-blockers:** The IOP-lowering efficacy and safety of AZOPT® 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 pre-dose IOP measurement of 24 mmHg to 36 mmHg. When dosed adjunctively to timolol 0.5% BID, AZOPT® 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 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).

**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.
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 AZOPT® 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 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.
BIBLIOGRAPHY


