SCHEDULING STATUS: S3

PROPRIETARY NAME (AND DOSAGE FORM)
AZOPTIC Eye Drops (Suspension)

COMPOSITION
AZOPTIC Eye Drops is a sterile, aqueous suspension containing 10 mg brinzolamide per ml with benzalkonium chloride 0.01% (m/v) as preservative. It is formulated to be readily suspended with slow settling following shaking, with a pH of approximately 7.5 and an osmolality of 300 mOsm/kg. Inactive ingredients are mannitol, carbomer 974P, tyloxapol, edetate disodium, sodium chloride, hydrochloric acid and/or sodium hydroxide (to adjust pH), and purified water.

PHARMACOLOGICAL CLASSIFICATION
A.15.4 Ophthalmic preparations, other.

PHARMACOLOGICAL ACTION
Carbonic anhydrase (CA) is an enzyme found in many tissues of the body including the eye. It catalyses the reversible reaction involving the hydration of carbon dioxide and the dehydration of carbonic acid. It exists as a number of isoenzymes, the most active being carbonic anhydrase II (CA-II), found primarily in red blood cells, 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.
Brinzolamide is an inhibitor of carbonic anhydrase II with an *in vitro* IC_{50} of 3.2 nM and a K_i of 0.13 nM against carbonic anhydrase-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.
Pharmacokinetic properties
Brinzolamide is absorbed into the systemic circulation following topical ocular administration. It distributes extensively into the red blood cells and exhibits a long half-life in whole blood (mean of approximately 24 weeks). The metabolite N-desethyl brinzolamide is formed, which binds mainly to carbonic anhydrase-I in the presence of brinzolamide and accumulates in red blood cells. In plasma, both parent drug and N-desethyl brinzolamide concentrations are low and generally below assay quantitation limits (<7.5 ng/ml). Binding to plasma proteins is not extensive (about 60%). Brinzolamide is eliminated by both renal excretion (about 60%) and hepatic metabolism (about 40%). Brinzolamide and N-desethyl are the predominant components in the urine along with trace levels of the N-desmethoxypropyl and O-desmethyl metabolites.
Following long-term administration of AZOPTIC, the inhibition of total red blood cell carbonic anhydrase activity is approximately 40-70% of predose levels. In patients with moderate renal function impairment, prolonged administration of oral brinzolamide resulted in increased red blood cell concentrations of N-desethyl brinzolamide and decreased total red blood cell CA activity with decreasing creatinine clearance. Brinzolamide red blood cell concentrations and CA-II activity remained unchanged. Inhibition of total CA activity was less than 90%. There is no information on the kinetics in patients with severe renal impairment.

INDICATIONS
AZOPTIC is indicated as monotherapy, or as adjunctive therapy to beta-blockers in the treatment of elevated intraocular pressure in ocular hypertension, or open-angle glaucoma.

CONTRA-INDICATIONS

- Hypersensitivity to any component of this product
- Hypersensitivity to sulphonamides (*see also Warnings section*)
- Severe renal impairment (CrCl<30 ml/min)
- Hyperchloraemic acidosis
- Concomitant therapy with oral carbonic anhydrase inhibitors
- Safety in pregnancy and lactation has not been established

WARNINGS

Brinzolamide is a sulphonamide and although administered topically, is absorbed systemically. Therefore, the same types of adverse reactions that are attributable to sulphonamides may occur with AZOPTIC. If signs of serious reactions or hypersensitivity occur, discontinue the use of this preparation.

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 AZOPTIC. The concomitant administration of AZOPTIC and oral carbonic anhydrase inhibitors is not recommended.

AZOPTIC has not been studied in patients with hepatic impairment and is therefore not recommended in such patients.

There is limited experience with AZOPTIC in the treatment of patients with pseudoexfoliative glaucoma or pigmentary glaucoma.

AZOPTIC was primarily evaluated in concomitant administration with timolol during adjunctive glaucoma therapy. Therefore, there are limited data regarding the administration of brinzolamide with other antiglaucomatous agents.

AZOPTIC has not been studied in patients with narrow-angle glaucoma.

The possible role of brinzolamide on corneal endothelial function has not been investigated in patients with compromised corneas (particularly in patients with low endothelial cell count). Specifically, 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, careful monitoring is recommended.

Benzalkonium chloride, which is commonly used as a preservative in ophthalmic products, has been reported to cause punctate keratopathy and/or toxic ulcerative keratopathy. Since AZOPTIC contains benzalkonium chloride, close monitoring is required with frequent or prolonged use in dry eye patients, or in conditions where the cornea is compromised.

AZOPTIC has not been studied in patients wearing contact lenses. AZOPTIC contains the preservative benzalkonium chloride, which may be adsorbed by soft contact lenses. Therefore, patients must be instructed to wait 15 minutes after instillation of AZOPTIC before inserting contact lenses. AZOPTIC must not be administered while wearing contact lenses.

Potential rebound effects following cessation of treatment with AZOPTIC have not been studied; the IOP-lowering effect is expected to last for 5-7 days.

Oral carbonic anhydrase inhibitors may impair the ability to perform tasks requiring mental alertness and/or physical coordination in elderly patients. AZOPTIC is absorbed systemically and therefore this may occur with topical administration.

Paediatric Use:

The safety and effectiveness of AZOPTIC in paediatric patients have not been established.

Effects on Ability to Drive and to Use Machines

Temporary blurred vision or other visual disturbances may affect the ability to drive or use machines. If transient blurring of vision occurs upon instillation, the patient should wait until the vision clears before driving or operating machinery.

Interactions with Other Medicines and Other Forms of Interaction

Acid-base disturbances have been reported with oral carbonic anhydrase inhibitors and have resulted in drug interactions (e.g., toxicity associated with high-dose salicylate therapy). Brinzolamide is a carbonic anhydrase inhibitor and although administered topically, is

absorbed systemically. Therefore, the potential for such drug interactions should be considered in patients receiving AZOPTIC.
Brinzolamide is metabolised in the liver by multiple cytochrome P-450 isoenzymes, including CYP3A4. Therefore, CYP3A4 inhibitors such as ketoconazole, itraconazole, clotrimazole, ritonavir and troleandomycin may inhibit the metabolism of brinzolamide and caution is advised if such inhibitors are given concomitantly. Specific interaction studies with other medicinal products have not been performed with AZOPTIC. AZOPTIC was used with ophthalmic timolol preparations without evidence of adverse reactions. An association between AZOPTIC and miotics or adrenergic agonists or other antiglaucoma agents than timolol has not been evaluated.

DOSAGE AND DIRECTIONS FOR USE

SHAKE WELL BEFORE USE.
When used as monotherapy or adjunctive therapy, the dose is one drop of AZOPTIC in the conjunctival sac of the affected eye(s) twice daily. Some patients may have a better response with one drop three times a day.
When substituting AZOPTIC for another ophthalmic antiglaucoma agent, discontinue the other agent after proper dosing for one day, and start AZOPTIC on the next day.
If more than one topical ophthalmic drug is being used, the drugs should be administered at least ten minutes apart.
Patients should be instructed to avoid allowing the tip of the dispensing container to contact the eye or surrounding structures or with other surfaces.
Nasolacrimal occlusion or gently closing the eyelids after instillation is recommended. This may reduce the systemic absorption of medication administered via the ocular route and result in a decrease in systemic side-effects.

Contact Lenses

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

Elderly Use:

The probability of having a side-effect with AZOPTIC is independent of age. No dosage alteration in elderly patients is therefore necessary.

SIDE-EFFECTS AND SPECIAL PRECAUTIONS

The most frequent treatment related side-effects and local symptoms that may be experienced are taste perversion (bitter, sour or unusual taste) (5.4%) and temporary blurred vision upon instillation, lasting from a few seconds to a few minutes (5.0%) (see also *Effects on ability to drive or use machinery*).
The following adverse reactions that were definitely, probably or possibly related to treatment have been reported. Their incidence was either common (less than 10%), uncommon (less than 1%) or rare (less than 0.1%).

Ocular Effects

Common: blurred vision (temporary blurring upon instillation, lasting from a few seconds to a few minutes), ocular discomfort (transient burning or stinging upon instillation), foreign body sensation, ocular hyperaemia and dry eye.
Uncommon: ocular pain, ocular discharge, ocular pruritis, keratitis, blepharitis, conjunctivitis, lid margin crusting, sticky sensation, tearing, eye fatigue, keratopathy, and abnormal vision.
Rare: keratoconjunctivitis, corneal staining, eye disorder, photophobia, meibomitis, vision change, irritation, glare, lid disorder, decreased vision and corneal erosion.

Systemic Effects

Brinzolamide is a sulphonamide and although administered topically, is absorbed systemically. Therefore, the same types of adverse reactions that are attributable to sulphonamides may occur with AZOPTIC (class effect) (*see also Warnings section*).
Taste perversion (bitter or unusual taste in the mouth following instillation) is the most frequently reported systemic side-effect reported with the use of AZOPTIC. It is likely caused

by passage of the eye drops in the nasopharynx via the nasolacrimal canal. Nasolacrimal occlusion or closing the eyelid for 3 minutes may help to reduce the incidence of this effect.
Body as a whole: *Uncommon*: chest pain, alopecia. *Rare*: pain.
Gastrointestinal Effects: *Common*: taste perversion. *Uncommon*: dry mouth, nausea and dyspepsia. *Rare*: diarrhoea and gastrointestinal disorder.
Hypersensitivity Reactions: *Uncommon*: dermatitis. *Rare*: urticaria, pruritus.
Nervous System Effects: *Common*: headache. *Uncommon*: paraesthesia characterised as numbness and a tingling sensation of the extremities, depression and dizziness. *Rare*: dream abnormality, hypertonia, agitation, amnesia, depersonalisation, nervousness, asthenia, insomnia, and tinnitus.
Respiratory Effects: *Uncommon*: rhinitis, dyspnoea, pharyngitis, and bronchitis. *Rare*: dry nose, epistaxis, and increased cough.
Urogenital Effects: *Rare*: kidney pain and impotence.
The following additional adverse reactions have been rarely reported from post-marketing experience with AZOPTIC. They are generally known adverse effects as related to the use of oral carbonic anhydrase inhibitors: abnormal liver function, malaise, somnolence, vomiting and increased urinary frequency.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

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. Treatment should be symptomatic and supportive.

IDENTIFICATION

Colourless to off-white suspension.

PRESENTATION

Natural (colourless) plastic DROP-TAINER® dispenser containing 5 ml or 10 ml, with a white polypropylene cap.

STORAGE INSTRUCTIONS

Store between 4°C to 25°C.
DO NOT USE MORE THAN 30 DAYS AFTER OPENING.
KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER 34/15.4/0382

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