NOVARTIS

AZOPTIC Eye Drops

(suspension)

Professional Information

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SCHEDULING STATUS

S3

1 NAME OF THE MEDICINE

AZOPTIC Eye Drops (suspension)

2 QUALITIVE AND QUANTITIVE COMPOSITION

AZOPTIC Eye Drops is a sterile, aqueous suspension containing 10 mg brinzolamide per ml

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.

Preservative: benzalkonium chloride 0.01 % (*m/v*)

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Colourless to off-white suspension

4 CLINICAL PARTICULARS

4.1 Therapeutic 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.

4.2 Posology and method of administration

Posology

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.

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.

Special populations

Elderly Use:

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

Hepatic and renal impairment:

AZOPTIC has not been studied in patients with hepatic impairment and is therefore not recommended in such patients. Brinzolamide has not been studied in patients with severe renal impairment (creatinine clearance < 30 mL/min/1.73 m^2). Since brinzolamide and its major metabolite are excreted predominately by the kidney, brinzolamide is therefore contraindicated in such patients (see section 4.3). However, in patients with moderate renal impairment (creatinine clearance 30-60 mL/min/1.73 m^2) there is no need for dose adjustments with topical administration of AZOPTIC.

Paediatric population

The safety and effectiveness of AZOPTIC in paediatric patients and children under the age of 18 years have not been established.

Method of administration

- For ocular use.
- 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.

4.3 Contraindications

- Hypersensitivity to any component of this product.
- Hypersensitivity to sulphonamides (*see section 4.4*)
- 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

4.4 Special warnings and precautions for use

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.

4.5 Interaction 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 (i.e. NSAIDs and salicylates) 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.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/ Contraception in males and females

No information available.

Pregnancy

There are no or limited amount of data from the use of ophthalmic brinzolamide as contained in AZOPTIC in pregnant women. Studies in animals with brinzolamide have shown reproductive toxicity following systemic administration.

AZOPTIC is not recommended during pregnancy and in women of childbearing potential not using contraception.

Breastfeeding

It is unknown whether brinzolamide/metabolites are excreted in human milk following topical ocular administration; however, a risk to the suckling child cannot be excluded. In animal studies following oral administration, minimal levels of brinzolamide were detected in breastmilk.

AZOPTIC is not recommended during breastfeeding.

Fertility

Studies have not been performed to evaluate the effect of topical ocular administration of AZOPTIC on male or female fertility. No effect on fertility was observed in rats after oral administration of brinzolamide.

4.7 Effects on ability to drive and use machines

Temporary blurred vision or other visual disturbances may affect mental and/or physical abilities to perform or execute tasks or activities requiring mental alertness, judgment and/or sound coordination, vision and 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.

4.8 Undesirable effects

a. Summary of the safety profile

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 section 4.7)*.

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 section 4.4*)

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.

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 %).

Tabulated list of adverse reactions

Body System	**Undesirable effect**		
	Common	Uncommon	Rare
Psychiatric disorders:		depression	
Nervous system disorders:		headache paraesthesia characterised as numbness and a tingling sensation of the extremities, dizziness.	dream abnormality, hypertonia, agitation, amnesia, depersonalisation, nervousness, asthenia, insomnia, and tinnitus.

Eye disorders:	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, eye irritation, eye pain	ocular pain, ocular discharge, ocular pruritis, keratitis, blepharitis, conjunctivitis, lid margin crusting, sticky sensation, tearing, eye fatigue, keratopathy, and abnormal vision, corneal erosion photophobia, dry eye, asthenopia, eye pruritis, increased lacrimation, eye discharge, eyelid margin crusting, punctuate keratitis, allergic conjunctivitis.	keratoconjunctivitis, corneal staining, eye disorder, meibomitis, vision change, irritation, glare, lid disorder, decreased vision, corneal oedema, hypoaesthesia eye, periorbital oedema
Ear and labyrinth disorders:			tinnitus
Cardiac disorders:			angina pectoris, heart rate irregular
Respiratory, thoracic and mediastinal disorders:		rhinitis, dyspnoea, pharyngitis, and bronchitis, epistaxis, rhinorrhoea, oropharyngeal pain, upper airway cough syndrome, throat irritation	dry nose, epistaxis, and increased cough, bronchial hyperreactivity, upper-respiratory tract congestion, sinus congestion, nasal congestion,
Gastrointestinal disorders:	taste perversion	dry mouth, nausea and dyspepsia diarrhoea, gastrointestinal disorder	
Skin and subcutaneous tissue disorders:		dermatitis	urticaria, pruritus alopecia
Renal and urinary disorders:			kidney pain and impotence

General disorders and administrative site conditions:		fatigue	Pain, chest pain feeling jittery, asthenia, irritability

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.

Body System	**Undesirable effect –Frequency not known**
Metabolism and nutrition disorders:	Decreased appetite
Nervous system disorders:	Somnolence, hypoaesthesia
Vascular disorders:	Decreased blood pressure
Gastrointestinal disorders:	vomiting
Hepato-biliary disorders:	abnormal liver function
Musculoskeletal, connective tissue and bone disorders:	Arthralgia
Renal and urinary disorders:	increased urinary frequency
General disorders and administrative site conditions:	malaise

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the "Report Drug Reaction Process", found online under SAHPRA's safety publications:

https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

In overdose, side effects can be precipitated and/or be of increased severity (*see section 4.8)*.

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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A.15.4 Ophthalmic preparations, other

Pharmacotherapeutic group: Antiglaucoma preparations and miotics, carbonic anhydrase inhibitors, ATC code: S01EC04

Mechanism of 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* IC50 of 3.2 nM and a Ki 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.

5.2 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 primarily by renal excretion (about 60 %). About 20 % is excreted in the urine as metabolites.

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 brinzolamide, 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 of brinzolamide in patients with severe renal impairment.

5.3 Preclinical safety data

Animal studies using brinzolamide showed no teratogenicity at doses up to 18 mg/kg/day and 6 mg/kg/day in rats and rabbits respectively. Decrease in foetal body weight and an increase in developmental variations in rats were observed at an oral dose of 18 mg/kg/day (375 times recommended human ophthalmic dose).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Benzalkonium chloride

Mannitol (E421)

Carbomer 974P

Tyloxapol

Edetate disodium

Sodium chloride

Hydrochloric acid/sodium hydroxide (to adjust pH)

Purified water

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years.

4 weeks after first opening

6.4 Special precautions for storage

Store between 4 °C to 25 °C.

Do not use for more than 30 days after opening.

Store in the original package/container.

6.5 Nature and contents of container

Natural (colourless) plastic bottle dispenser containing 5 ml or 10 ml, with a white polypropylene cap.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicine or waste materials derived from such medicine and other handling of the product

No special requirements.

7 THE HOLDER OF THE CERTIFICATE OF REGISTRATION

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