PROFESSIONAL INFORMATION

SCHEDULING STATUS:

S3

1. NAME OF THE MEDICINE

AZIBRIN 1 %

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL of suspension contains 10 mg brinzolamide.

Contains sugar alcohol: Mannitol 33,00 mg/mL

Contains preservative: Benzalkonium chloride 0,02 % *w/v*

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Opthalmic suspension

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

AZIBRIN 1 % 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

When used as monotherapy or adjunctive therapy, the dose is one drop of AZIBRIN 1 % 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 AZIBRIN 1 % for another ophthalmic antiglaucoma medicine, discontinue the other medicine after proper dosing for one day, and start AZIBRIN 1 % on the next day.

If more than one topical ophthalmic medicine is being used, the medicines should be administered at least ten minutes apart.

Contact Lenses

The preservative in AZIBRIN 1 %, benzalkonium chloride, may be absorbed by soft contact lenses. Contact lenses should be removed during instillation of AZIBRIN 1 % but may be reinserted 15 minutes after instillation.

Special populations

Elderly Use:

The probability of having a side-effect with AZIBRIN 1 % is independent of age. No dosage alteration in elderly patients is therefore necessary.

Method of administration

AZIBRIN 1 % is for ocular administration.

SHAKE WELL BEFORE 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.

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4.3. Contraindications

- Hypersensitivity to brinzolamide or to any of the excipients of this medicine listed in section 6.1.
- 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 AZIBRIN 1 %. 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 AZIBRIN 1 %.
The concomitant administration of AZIBRIN 1 % and oral carbonic anhydrase inhibitors is not recommended.

Brinzolamide has not been reported to be studied in patients with hepatic impairment and is therefore not recommended in such patients.
There is limited experience reported with brinzolamide in the treatment of patients with

pseudoexfoliative glaucoma or pigmentary glaucoma.

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

Brinzolamide as contained in AZIBRIN 1 % has not been reported to be studied in patients with narrow-angle glaucoma.

The possible role of brinzolamide on corneal endothelial function has not been reported in patients with compromised corneas (particularly in patients with low endothelial cell count). Specifically, patients wearing contact lenses have not been reported to be 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 frequently used as a preservative in ophthalmic products, has been reported to cause punctate keratopathy and/or toxic ulcerative keratopathy. Since AZIBRIN 1 % contains benzalkonium chloride, close monitoring is required with frequent or prolonged use in dry eye patients, or in conditions where the cornea is compromised.

Brinzolamide as contained in AZIBRIN 1 % has not been reported to be studied in patients wearing contact lenses.

AZIBRIN 1 % 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 AZIBRIN 1 % before

inserting contact lenses. AZIBRIN 1 % must not be administered while wearing contact lenses.

Potential rebound effects following cessation of treatment with brinzolamide have not been reported to be 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. AZIBRIN 1 % is absorbed systemically and therefore this may occur with topical administration.

Paediatric Use:

The safety and effectiveness of AZIBRIN 1 % in paediatric patients and children under the age of 18 years have not been established.

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 as contained in AZIBRIN 1 % 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 AZIBRIN 1 %.

- 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.

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- Specific interaction studies with other medicines have not been reported with brinzolamide. Brinzolamide has been reported to be used with ophthalmic timolol preparations without evidence of adverse reactions. An association between brinzolamide as contained in AZIBRIN 1 % and miotics or adrenergic agonists or other antiglaucoma medicines than timolol has not been reported.

4.6. Fertility, pregnancy and lactation

Pregnancy

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

AZIBRIN 1 % is not recommended during pregnancy and in women of childbearing potential not using contraception.

Breast-feeding

It is unknown whether brinzolamide/metabolites are reported to be excreted in human milk following topical ocular administration. Animal studies have reported the excretion of minimal levels of brinzolamide in breast milk following oral administration.

AZIBRIN 1 % is not recommended during breastfeeding.

Fertility

Animal studies with brinzolamide reported no effect on fertility. Studies have not been reported to evaluate the effect of topical ocular administration of brinzolamide on human fertility.

4.7. Effects on ability to drive and use machines

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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.

4.8 Undesirable effects

The most frequent reported treatment-related adverse reactions and local symptoms that may be experienced are: dysgeusia (bitter or unusual taste, see description below) and temporary blurred vision upon instillation, lasting from a few seconds to a few minutes (see 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 AZIBRIN 1 % (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 AZIBRIN 1 %. 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.

Tabulated summary of adverse reactions

The following adverse reactions have been reported with brinzolamide as contained in AZIBRIN 1 % 10 mg/mL eye drops, suspension and are classified according to the following convention: frequent, less frequent or frequency not known (cannot be estimated from the reported data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

System Organ Class	Frequent	Less frequent	Frequency not

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			known
Infections and infestations		Naso-pharyngitis, pharyngitis, sinusitis	Rhinitis
Blood and lymphatic system disorders		Red blood cell count decreased, blood chloride increased	
Immune system disorders			Hypersensitivity
Metabolism and nutritional disorders			Decreased appetite
Psychiatric disorders		Apathy, depression, depressed mood, libido decreased, nightmare	
Nervous system disorders		Memory impairment, motor dysfunction, dizziness, headache, paraesthesia, somnolence, hypertonia, amnesia	tremor, hypoaesthesia, ageusia, nervousness, insomnia, agitation, dream abnormality, depersonalisation
Eye disorders	blurred vision, eye irritation, eye	corneal erosion, keratitis, punctate keratitis,	corneal disorder, visual disturbance,

	pain, foreign body sensation in eyes, ocular hyperaemia, ocular discomfort, dry eye	keratopathy, deposit eye, corneal epithelium defect, corneal epithelium disorder, blepharitis, eye pruritus, conjunctivitis, eye swelling, photophobiadry eye, allergic conjunctivitis, pterygium, scleral pigmentation, asthenopia, abnormal sensation in eye, keratoconjunctivitis sicca, subconjunctival cyst, conjunctival hyperaemia, eyelids pruritus, eye discharge, eyelid margin crusting, lacrimation increased, diplopia, visual acuity reduced, photopsia, intraocular pressure increased, optic nerve cup/disc ratio increased, eyelid disorder	eye allergy, madarosis, erythema of eyelid, hypoaesthesia eye, periorbital oedema, corneal oedema, corneal staining, meibomianitis, glare
Ear and labyrinth disorders		tinnitus	vertigo

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Cardiac disorders		Cardio-respiratory distress, bradycardia, palpitations	Dysrhythmia, tachycardia, hypertension, blood pressure increased, blood pressure decreased, heart rate increased, angina pectoris, heart rate irregular
Respiratory, thoracic and mediastinal disorders		Dyspnoea, bronchitis, oropharyngeal pain, pharyngo-laryngeal pain, throat irritation, upper airway cough rhinorrhoea, sneezing	Asthma, epistaxis, bronchial hyperreactivity, upper respiratory tract congestion, sinus congestion, nasal congestion, increased cough, nasal dryness
Gastro-intestinal disorders	Dysgeusia	Oesophagitis, diarrhoea, nausea, vomiting, dyspepsia, upper abdominal pain, abdominal	

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		discomfort, stomach discomfort, flatulence, frequent bowel movements, gastrointestinal disorder, hypoaesthesia oral, paraesthesia oral, dry mouth	
Hepato-biliary disorders			Liver function test abnormal
Skin and subcutaneous tissue disorders		Rash, rash maculo-papular, skin tightness, dermatitis	Erythema, urticaria, alopecia, pruritus generalised
Musculo-skeletal and connective tissue disorders		Back pain, muscle spasms, myalgia	Arthralgia, pain in extremity
Renal and urinary disorders			Pollakiuria, Renal pain
Reproductive system and breast disorders		Erectile dysfunction, impotence	
General disorders and administration site		Pain, chest discomfort, fatigue, feeling abnormal	Peripheral x oedema, malaise, chest

conditions			pain, feeling jittery, asthenia, irritability
Injury, poisoning and procedural complications	Foreign body sensation in eye		

Description of selected adverse events

Dysgeusia (bitter or unusual taste in the mouth following instillation) was the most frequently reported systemic adverse reaction associated with the use of brinzolamide. It is likely caused by passage of the eye drops in the nasopharynx via the nasolacrimal canal. Nasolacrimal occlusion or gently closing the eyelid after instillation may help reduce the incidence of this effect (see section 4.2).

Brinzolamide is a sulphonamide inhibitor of carbonic anhydrase with systemic absorption. Gastrointestinal, nervous system, haematological, renal and metabolic effects are generally associated with systemic carbonic anhydrase inhibitors. The same type of adverse reactions that are attributable to oral carbonic anhydrase inhibitors may occur with topical administration.

No unexpected adverse reactions have been reported with brinzolamide when used as adjunctive therapy to travoprost. The adverse reactions seen with the adjunctive therapy have been reported with each active substance alone.

Paediatric population

In reported small short-term clinical trials, approximately 12,5 % of paediatric patients reported adverse reactions, the majority of which were local, non-serious ocular reactions such as conjunctival hyperaemia, eye irritation, eye discharge, and lacrimation increased (see section 5.1).

Urogenital Effects

The following additional adverse reactions have been less frequently reported from post-marketing experience with brinzolamide. 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.

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. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the '**6.04 Adverse Drug Reaction Reporting form'**, found online under SAHPRA's publications:

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

4.9. Overdose

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

Pharmacological classification

A.15.4 Ophthalmic preparations, other.

Pharmacotherapeutic group: Antiglaucoma preparations and miotics, carbonic anhydrase inhibitors,

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ATC code: S01EC04

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.

5.2 Pharmacokinetic properties

Brinzolamide has been reported to be absorbed into the systemic circulation following topical ocular administration. It has been reported to be distributed 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 reported to be 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 brinzolamide, the inhibition of total red blood cell carbonic anhydrase activity is reported to be approximately 40-70 % of predose levels. In patients with moderate renal function impairment, prolonged administration of oral brinzolamide has been reported to result 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 reported to be less than 90 %. There is no information on the kinetics in patients with severe renal impairment.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Carbomer Homopolymer Type B (Carbopol 974P), Sodium Chloride (Parenteral grade), Mannitol, Tyloxapol, Edetate disodium, Benzalkonium chloride solution (50 %), Water for Injection, Sodium Hydroxide, Hydrochloric acid.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store below 25 °C.

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DO NOT USE MORE THAN 30 DAYS AFTER OPENING.

KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container

AZIBRIN 1 % Ophthalmic Suspension w/v, 5ml is available in a 5 mL LDPE sterile dropper bottle, plugged with 13 mm LDPE sterile plug and capped with 13 mm white, opaque HDPE pilfer proof sterile cap for dropper bottle.

Each bottle is labeled with printed sticker label and packed in a show box along with pack insert.

6.6 Special precautions for disposal and other

No special requirements. Any unused medicinal product or waste material should be disposed of in accordance with local requirements

7. HOLDER OF CERTIFICATE OF REGISTRATION

Ranbaxy Pharmaceuticals (Pty) Ltd

14 Lautre Road

Stormill Ext.1

Roodepoort

Johannesburg

8. REGISTRATION NUMBER

53/15.4/0249

9. DATE OF FIRST AUTHORISATION

PROFESSIONAL INFORMATION

23 January 2024

10. DATE OF REVISION OF THE TEXT