AUSTRALIAN PRODUCT INFORMATION – BRINZOQUIN 1.0% (BRINZOLAMIDE) EYE DROPS

1 NAME OF THE MEDICINE

Brinzolamide

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

The eye drops suspension contains 10 mg/mL (1%) brinzolamide and also 0.1 mg/1 mL benzalkonium chloride as a preservative.

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Eye drops.

BrinzoQuin is a white to off-white, uniform suspension.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

BrinzoQuin Eye Drops 1.0% are indicated to decrease intraocular pressure in:

- ocular hypertension
- open-angle glaucoma

4.2 DOSE AND METHOD OF ADMINISTRATION

The recommended dosage is one drop of BrinzoQuin in the conjunctival sac of the affected eye(s) twice daily.

When substituting for another ophthalmic anti-glaucoma agent with BrinzoQuin, the other agent should be discontinued and BrinzoQuin should be started on the following day.

Concomitant therapy

BrinzoQuin has been used concomitantly with other agents e.g. travoprost, latanoprost, timolol (see Section 5.1 Parmacodynamic Properties – Clinical Trials). In case of concomitant therapy with more than one topical ophthalmic medicinal product being used, the eye drops must be administered with an interval of at least five minutes. Eye ointments should be administered last.

Method of Administration

For ocular use. Patients should be instructed to shake the bottle well prior to use.

To avoid contamination, the dropper tip should not touch any surface. The dropper tip should also not come into contact with the eye as this may cause injury to the eye. Patients should be instructed to keep the bottle tightly closed when not in use.

Instillation of eye drops may cause initial discomfort (see Section 4.8 Adverse effects (Undesirable effects)).

Nasolacrimal occlusion and closing the eyelid for two minutes, after instillation is recommended. This may result in a decrease in systemic side effects and an increase in local activity.

Patients must be instructed to remove soft contact lenses prior to application of BrinzoQuin and to wait fifteen minutes after instillation of the dose before reinsertion.

4.3 CONTRAINDICATIONS

BrinzoQuin is contraindicated in patients with a known hypersensitivity to brinzolamide, sulfonamides or any of the excipients in the product (see Section 6.1 List of excipients).

BrinzoQuin is also contraindicated in patients with severe renal impairment and in patients with hyperchloraemic acidosis.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Not for injection or oral ingestion

The management of patients with acute angle-closure glaucoma requires therapeutic interventions in addition to ocular hypotensive agents. BrinzoQuin has not been studied in patients with acute angle-closure glaucoma.

Brinzolamide is a sulfonamide and, although administered topically, is absorbed systemically. The same types of adverse reactions or hypersensitivity that are attributable to sulfonamides may, therefore, occur with topical administration. Hypersensitivity reactions reported with sulfonamide derivatives, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), can occur in patients receiving BrinzoQuin. At the time of prescription, patient should be advised of the signs and symptoms and monitored closely for skin reactions. BrinzoQuin should be discontinued immediately if signs of serious reactions or hypersensitivity occur.

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 BrinzoQuin. The concomitant administration of BrinzoQuin and oral carbonic anhydrase inhibitors has not been studied and is not recommended.

Acid-base disturbances have been reported with oral carbonic anhydrase inhibitors. BrinzoQuin should be used with caution in patients with risk of renal impairment because of the possible risk of metabolic acidosis.

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). Carbonic anhydrase inhibitors may affect corneal hydration, which may lead to a corneal decompensation and

oedema. Careful monitoring of patients with compromised corneas, such as patients with diabetes mellitus or corneal dystrophies, is recommended.

BrinzoQuin contains benzalkonium chloride which may cause eye irritation and is known to discolour soft contact lenses. Avoid contact with soft contact lenses. Patients must be instructed to remove contact lenses prior to application of BrinzoQuin and wait at least 15 minutes before reinsertion.

Contact Lenses

If patients continue to wear soft (hydrophilic) contact lenses while under treatment with BrinzoQuin, they should remove their lens(es) *prior* to instilling BrinzoQuin in the affected eye(s) and should not insert their lens(es) until 15 minutes after instillation of the eye drops.

Use in hepatic impairment

BrinzoQuin has not been studied in patients with hepatic impairment. Caution should, therefore, be exercised if a decision is made to commence therapy with BrinzoQuin in such patients.

Use in renal impairment

BrinzoQuin has not been studied in patients with severe renal impairment (CrCl < 30 mL/min) or in patients with hyperchloraemic acidosis. Brinzolamide and its main metabolite are predominantly excreted by the kidney; BrinzoQuin is, therefore, contraindicated in such patients (see Section 4.3 Contraindications).

Use in the elderly

In clinical studies conducted with brinzolamide 1.0%, the probability of having an adverse reaction was independent of age. No differences in patients experiencing adverse reactions were noted when patients less than 65 years of age were compared to patients greater than 65 years of age. There are no modifications to the recommended dosing regimen for elderly patients.

Paediatric use

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

Effects on laboratory tests

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Specific drug interaction studies have not been performed with BrinzoQuin. In clinical studies, however, brinzolamide 1.0% were used concomitantly with the following medications without evidence of adverse interactions:

- timolol maleate eye drops, systemic medications including ACE inhibitors, calcium-channel blockers, diuretics, non-steroidal anti-inflammatory drugs including aspirin, and hormones (e.g. oestrogen, insulin, thyroxine).

Association between BrinzoQuin and miotics or adrenergic agonists has not been fully evaluated during adjunctive glaucoma therapy.

Brinzolamide is a carbonic anhydrase inhibitor and, although administered topically, is absorbed systemically. In clinical studies, brinzolamide was not associated with acid-base disturbances. These

disturbances have, however, been reported with oral carbonic anhydrase inhibitors and have, in some instances, resulted in drug interactions (e.g. nonsteroidal anti-inflammatory drugs (NSAIDs) and toxicity associated with high-dose salicylate therapy). The potential for such drug interactions should, therefore, be considered in patients receiving BrinzoQuin.

There is potential for an additive effect on the known systemic effects of carbonic anhydrase inhibition in patients receiving an oral carbonic anhydrase inhibitor and BrinzoQuin. The concomitant administration of BrinzoQuin and oral carbonic anhydrase inhibitors is not recommended.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

A fertility and early embryonic study, in which male and female rats were dosed by oral gavage with brinzolamide at doses up to 18 mg/kg/day, showed no effects on fertility or reproductive capacity. Studies have not been performed to evaluate the effect of topical ocular administration of brinzolamide on human fertility.

Use in pregnancy – Pregnancy Category B3

Studies in animals with brinzolamide have shown reproductive toxicity following systemic administration. Radioactivity was found to cross the placenta and was present in the foetal tissues and blood following oral administration of ^{14}C-brinzolamide to pregnant rats.

Developmental toxicity studies in rabbits at oral doses up to 6 mg/kg/day brinzolamide produced maternal toxicity at 6 mg/kg/day and a significant increase in the number of foetal variations, such as accessory skull bones; at 1 and 6 mg/kg/day the incidence was only slightly higher than seen historically. In rats, statistically significant decreased body weights of foetuses 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. No treatment-related malformations were seen.

No studies of the use of ophthalmic brinzolamide have been conducted in pregnant women. BrinzoQuin should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

Use in lactation

Studies in animals have shown that following oral administration brinzolamide is excreted in breast milk. Following oral administration of ^{14}C-brinzolamide to lactating rats, radioactivity was found in milk at concentrations below those in the blood and plasma. Decreases in pup bodyweights were observed at 15 mg/kg/day in a pre-and postnatal study in which rats were given brinzolamide by oral gavage at doses up to 15 mg/kg/day.

It is not known whether brinzolamide is transferred into human milk following topical ocular administration. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from brinzolamide, 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.

The developmental and health benefits of breast-feeding should be considered along with the mother's clinical need for BrinzoQuin and any potential adverse effects on the breast-fed child from BrinzoQuin.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

As with other ophthalmic medications, patients should be advised to exercise caution if they experience transient blurred vision or other visual disturbances following instillation of eye drops; patients should wait until their vision clears before driving or using machinery.

Additionally, nervous system disorders have been reported with the use of the product which may affect the ability to drive or use machines (see Section 4.8 Adverse effects (Undesirable effects)).

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

In well-controlled clinical studies, undesirable effects related to brinzolamide 1.0% were non-serious, generally mild to moderate, and usually did not lead to discontinuation of therapy. Tabulated adverse reaction data (considered to be possibly, probably or definitely related to treatment), providing comparisons to placebo and other active comparators (to an incidence 1% or greater), which have been generated from all clinical studies with brinzolamide 1.0%, are provided below.

Uncommon ophthalmic events (incidence <1% and ≥ 0.1%) not detailed in the table below included blepharitis, conjunctivitis, lid margin crusting, sticky sensation, eye fatigue, abnormal vision, keratopathy, keratoconjunctivitis, corneal staining, eye disorder, photophobia, diplopia, meibomitis, vision changes, irritation, glare and lid disorder.

Uncommon non-ocular events (incidence <1% and ≥ 0.1%) not detailed in Table 1 below included:

Body as a whole:	chest pain, asthenia and pain.
Digestive:	dry mouth, nausea, dyspepsia, diarrhoea, gastrointestinal disturbance.
Nervous:	paraesthesia, depression, dizziness, dream abnormality, hypertonia, agitation, amnesia, depersonalisation, nervousness.
Respiratory:	dyspnoea, pharyngitis, bronchitis, dry nose, epistaxis.
Skin and appendages:	dermatitis, alopecia, urticaria, pruritus.
Special senses:	tinnitus.
Urogenital:	kidney pain, impotence.

Table 1. Tabulated Adverse Reaction Data Comparing Incidence (%) Figure

Adverse Events	**Brinz 1.0%**	**Brinz 1.0% + Tim 0.5%**	**Dorz 2%**	**Tim 0.5%**	**Placebo**
	N = 1227	**N = 204**	**N = 524**	**N = 252**	**N = 116**
Ocular					
Blurred Vision	5.0	4.9	1.3	2.8	1.7
Discomfort	2.5	1.5	11.1	4.4	2.6
Foreign body sensation	1.8	1.0	0.6	0.8	-
Hyperaemia	1.2	0.5	1.9	0.8	0.9
Dry eye	1.1	-	0.4	-	0.9
Pain	1.0	0.5	0.4	1.2	0.9
Discharge	1.0	0.5	-	-	0.9
Pruritus	0.9	-	1.1	1.2	1.7
Keratitis	0.7	-	-	1.2	-
Tearing	0.2	-	1.3	-	-
Non-ocular					
<u>Body as a whole</u>					
Headache	1.3	0.5	1.3	0.8	0.9
<u>Respiratory</u>					
Rhinitis	0.2	-	1.0	-	-
Dyspnoea	0.2	-	-	2.0	-
Asthma	-	1.0	-	0.8	-
<u>Special Senses</u>					
Taste Perversion	5.5	4.4	5.2	-	0.9
Brinz = Brinzolamide Tim = Timolol maleate Dorz = Dorzolamide - = Not reported					

Post Marketing Experience

The following adverse reactions have been reported during clinical studies with BrinzoQuin and are classified according to the subsequent convention: very common (≥ 1/10), common (≥ 1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000) and very rare (<1/10,000). Within each frequency-grouping, adverse reactions are presented in order of decreasing seriousness.

Eye disorders

Common (≥ 1% to < 10%): vision blurred, eye irritation, eye pain, dry eye, eye discharge, ocular discomfort, ocular hyperaemia.

Uncommon (≥ 0.1% to < 1%): corneal erosion, punctate keratitis, keratitis, conjunctivitis, conjunctivitis allergic, blepharitis, visual acuity reduced, photophobia, asthenopia, periorbital oedema, eye pruritus, lacrimation increased, eyelid margin crusting.

Rare (≥ 0.01% to < 0.1%): corneal oedema, diplopia, reduced visual acuity, photopsia, hypoaesthesia eye, periorbital oedema.

Psychiatric disorders

Uncommon (≥ 0.1% to < 1%): depression.

Rare (≥ 0.01% to < 0.1%): insomnia.

Nervous system disorders

Common (≥ 1% to < 10%): headache, dysgeusia.

Uncommon (≥ 0.1% to < 1%): dizziness, paresthesia.

Rare (≥ 0.01% to < 0.1%): memory impairment, somnolence.

Cardiac disorders

Rare (≥ 0.01% to < 0.1%): angina pectoris, heart rate irregular.

Respiratory, thoracic and mediastinal disorders

Uncommon (≥ 0.1% to < 1%): dyspnoea, epistaxis, rhinorrhoea, oropharyngeal pain, upper airway cough syndrome, throat irritation.

Rare (≥ 0.01% to < 0.1%): bronchial hyperreactivity, upper respiratory tract congestion, sinus congestion, nasal congestion, cough, nasal dryness.

Gastrointestinal disorders

Uncommon (≥ 0.1% to < 1%): nausea, diarrhoea, dyspepsia, abdominal discomfort, dry mouth.

Skin and subcutaneous tissue disorders

Uncommon (≥ 0.1% to < 1%): rash.

Rare (≥ 0.01% to < 0.1%): urticaria, alopecia, pruritus generalised.

General disorders and administration site conditions

Uncommon (≥ 0.1% to < 1%): fatigue, irritability.

Rare (≥ 0.01% to < 0.1%): feeling jittery, asthenia.

Table 2. Adverse reactions from post-marketing surveillance (frequency not known)

System organ classification	Adverse reactions
Eye disorders	Medication residue
Ear and labyrinth disorders	Tinnitis
Nervous system disorders	Hypoaesthesia
Vascular disorders	Blood pressure decreased
Skin and subcutaneous tissue disorders	Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN)
Metabolism and nutrition disorders	Decreased appetite
Musculoskeletal and connective tissue disorders	Arthralgia
General disorders and administration site conditions	Chest pain

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

No information on systemic overdosage is available in humans. 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.

A topical overdose of BrinzoQuin may be flushed from the eyes with warm tap water.

In Australia, contact Poisons Information Centre on 13 11 26 for advice on management.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Brinzolamide is a carbonic anhydrase inhibitor. When instilled in the eye, BrinzoQuin has the action of reducing elevated intraocular pressure, whether or not accompanied by glaucoma.

Glaucoma is defined as an optic neuropathy resulting in optic nerve head damage and visual field loss. The pathogenesis of glaucoma is multi-factorial, however, the primary risk factors are considered to

be sustained elevated intraocular pressure and poor ocular perfusion. The ocular hypotensive action of brinzolamide is mediated through inhibition of carbonic anhydrase in the ciliary processes of the eye which decreases aqueous humour secretion, presumably by slowing the formation of bicarbonate ions with subsequent reduction in sodium and fluid transport.

Carbonic anhydrase is an enzyme found in many tissues of the body, including the eye. Carbonic anhydrase catalyses 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 CA-II, found primarily in red blood cells (RBCs), but also in other tissues. Brinzolamide is an inhibitor of carbonic anhydrase II (CA-II), which is the predominant iso-enzyme in the eye, 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 a low affinity for 34 receptors or second messenger systems, indicating selectivity for CA-II.

Clinical trials

In two randomised, double-masked studies of 3 month duration, monotherapy with brinzolamide eye drops 1.0% produced a significant reduction in intraocular pressure when dosed twice daily; this intraocular pressure reduction was equivalent to that of dorzolamide 2% dosed three times daily (see below). No additional clinically or statistically significant benefit was evident following administration of brinzolamide eye drops three times daily.

Table 3. Average Intraocular Pressure Reduction

% Reduction, Absolute Reduction in mm Hg (n)		
	10 AM	**6 PM**
Study 1		
Brinzolamide 1.0% twice daily*	-16.7%, -4.2 (109)	-15.3%, -3.7 (107)
Dorzolamide 2% three times daily*	-20.1%, -4.9 (112)	-18.2%, -4.3 (111)
Study 2		
Brinzolamide 1.0% twice daily*	-21.8%, -5.7 (144)	-18.9%, -4.8 (142)
Dorzolamide 2% three times daily*	-23.0%, -5.9 (146)	-21.2%, -5.4 (145)
Timolol maleate 0.5% twice daily*	-24.3%, -6.3 (61)	-21.4%, -5.5 (60)

*No clinically or statistically significant difference between treatments

In a long-term (18 month study) comparing brinzolamide 1.0% (n=94) with timolol maleate 0.5% (n=49; both twice daily), the mean absolute changes in intraocular pressure (mm Hg) at 18 months were -4.0 (95% CI: -4.6, -3.4) and -5.5 (95% CI: -6.4, -4.7) respectively. Eighty-one patients completed the study; the results indicated that the intraocular pressure lowering effect of brinzolamide 1.0% does not diminish over time.

Thirty volunteers with a diagnosis of asthma or chronic obstructive pulmonary disease were enrolled in a masked, cross-over design study to compare the acute effects of brinzolamide 1.0% versus timolol maleate 0.5% on pulmonary function as measured by forced expiratory volume in one second (FEV1). Within 15 minutes of the instillation of a single drop of timolol maleate 0.5%, statistically significant decreases in mean FEV1 were observed (compared to both baseline and brinzolamide 1.0%); these continued for up to 3 hours following instillation. No effect was observed on FEV1 following the instillation of brinzolamide 1.0%.

Two masked, well-controlled studies, each of one-week duration, were designed to compare the comfort of brinzolamide 1.0% twice daily to dorzolamide eye drops 2.0% three times daily. Each of these studies indicated that a significantly greater ($p<0.001$) percentage of patients experienced no discomfort following repeated instillation of brinzolamide 1.0%, as tabulated below.

Table 4. Percent Patients Experiencing No Discomfort (n)

	Brinzolamide eye drops 1.0% BID	**Dorzolamide eye drops 2.0% TID**
Study 4	71.2 (37)	19.6 (10)
Study 5	81.3 (39)	17.0 (8)

Concomitant therapy

Two Phase IV clinical studies assessed the efficacy and safety of brinzolamide when added concomitantly to prostaglandins (i.e. travoprost and latanoprost). The available data support a lowering of IOP when brinzolamide is added to these agents.

One 12-week, double-masked, randomised study in which 215 patients with ocular hypertension or primary open-angle glaucoma were enrolled, was conducted. A total of 201 patients were randomised and 192 were included in the per protocol analysis. The primary objective of the study was to compare the efficacy and safety of brinzolamide 1% and timolol 0.5%, each administered twice daily when added to travoprost 0.004% administered once daily in the evening. Patients who were considered inadequately controlled on monotherapy (travoprost, latanoprost or bimatoprost) were eligible to be enrolled in this study. The primary endpoint was mean diurnal IOP.

There was no statistically significant difference in mean diurnal IOP at 12 weeks between the treatment groups (18.1 mm Hg vs 18.1 mm Hg in the brinzolamide and timolol groups, respectively). The mean reductions in diurnal IOP were 3.4 mm Hg and 3.2 mm Hg for the brinzolamide and timolol groups, respectively. Overall, the efficacy of brinzolamide 1%, as concomitant therapy, was comparable to concomitant therapy with timolol 0.5%. There was a higher incidence of local adverse effects (conjunctival hyperaemia, burning or foreign body sensation) with brinzolamide than with timolol; however, the differences were not statistically significant.

A second, open-label 12-week study was conducted in 82 patients with open-angle glaucoma or ocular hypertension. A total of 79 patients were evaluable for the intent-to-treat analysis. Patients, requiring additional IOP-lowering from a baseline of travoprost eye drops, received brinzolamide 1% concomitantly. The primary efficacy endpoint was the mean reduction in IOP at 12 weeks.

There was a mean reduction of 3.9 mm Hg after 4 weeks and 4.2 mm Hg after 12 weeks. Overall, 43 patients (60.6%) had an IOP below 18 mm Hg at the conclusion of the study.

Additional studies have been published concerning IOP control (Tsukamoto *et al.* J. Ocular Pharmacol. Ther. 21:170-173, 2005, Tsukamoto *et al.* J. Ocular Pharmacol. Ther. 21: 395-399, 2005). These studies suggest that brinzolamide might be added to dual therapy (latanoprost plus beta blocker) or substituted for dorzolamide in triple therapy.

When used twice daily, adjunctively to timolol maleate 0.5% for 3 months, brinzolamide 1.0% provided an additional intraocular pressure lowering effect. This was equivalent to dorzolamide 2% dosed twice daily adjunctively to timolol maleate 0.5% (see below). No additional clinically or statistically significant benefit was evident following administration of brinzolamide 1.0% three times daily.

Table 5. Average Intraocular Pressure Reduction

% Reduction, Absolute Reduction in mm Hg (n)		
	9 AM	**11 PM**
Study 3		
Brinzolamide eye drops 1.0% twice daily*	-17.1%, -4.3 (101)	-19.9%, -4.9 (102)
Dorzolamide 2% three times daily*	-16.6%, -4.3 (105)	-20.8%, -5.0 (103)

*No clinically or statistically significant difference between treatments

During this study, up to 89.3% (at peak) receiving brinzolamide 1.0% in combination with timolol maleate 0.5% achieved an intraocular pressure reduction ≥ 5 mm Hg or had their intraocular pressure reduced to ≤ 21 mm Hg. These results were equivalent to those seen with dorzolamide eye drops 2.0% in combination with timolol maleate 0.5% (85.4%).

5.2 PHARMACOKINETIC PROPERTIES

Following topical ocular administration, brinzolamide is absorbed into the systemic circulation. Due to its high affinity for carbonic anhydrase II (CA-II), brinzolamide distributes extensively into the red blood cells (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 (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 the N-desmethoxypropyl and O-desmethyl metabolites.

An oral pharmacokinetic study was conducted in which healthy volunteers received 1 mg capsules of brinzolamide twice daily for up to 32 weeks. This regimen provided a higher systemic exposure rate than topical ocular administration of brinzolamide dosed in both eyes three times daily, and simulated

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 ranging from 6-30 µM. 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 healthy subjects.

An oral pharmacokinetic study was conducted in which subjects with mild to moderate renal impairment (creatinine clearance of 30-60 mL/minute) received 1 mg capsules of brinzolamide twice daily for up to 54 weeks. By week 4 of treatment, parent drug RBC concentrations ranged from approximately 20 to 40 µM and showed little subsequent change. At steady-state, parent drug and N-desethyl metabolite RBC concentrations ranged from 22.0 to 46.1 and 17.1 to 88.6 µM, respectively. Metabolite RBC concentrations, but not those of parent drug, showed a significant ($p<0.05$) increase with decreasing creatinine clearance. Total RBC CA activity, but not CA-II activity, showed a significant decrease as creatinine clearance decreased. In spite of the greater inhibition of total CA activity in subjects showing the highest degree of renal impairment, all subjects showed <90% total CA inhibition at steady-state. This is below the 99% or greater inhibition associated with systemic adverse effects.

In a topical ocular study, patients with open-angle glaucoma or ocular hypertension received brinzolamide 1.0% either two or three times daily for up to 18 months. Steady-state concentrations of brinzolamide were reached for most subjects within 6-9 months, while steady state for the N-desmethyl metabolite was reached within 12 to 18 months. At steady-state, brinzolamide RBC concentrations were similar to those found in the oral study, but levels of the N-desmethyl metabolite were lower. Carbonic anhydrase activity was approximately 40-70% of per-dose levels, indicating a degree of inhibition that was substantially lower than that observed orally and unlikely to elicit systemic side effects.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Genotoxicity studies with brinzolamide did not demonstrate any mutagenic potential in one *in vitro* (Ames assay) or chromosomal damage in an *in vivo* assay (micronucleus formation). Brinzolamide did induce forward mutations in the mouse lymphoma assay *in vitro*, with, but not without metabolic activation. Brinzolamide was negative in a sister chromatid exchange assay in mice.

Carcinogenicity

A two year bioassay, in which rats were dosed by oral gavage at doses up to 8 mg/kg/day brinzolamide revealed no evidence of a carcinogenic effect. A similar study conducted in mice (0, 1, 3 and 10 mg/kg/day brinzolamide dosed by oral gavage) also showed that brinzolamide was non-carcinogenic. The mouse study did, however, reveal a statistically significant increase in urinary bladder tumours in female mice given 10 mg/kg/day orally for 24 months. Dose-related proliferative changes in the urinary bladder were observed in female mice at all dose levels and among males at 10 mg/kg/day. The elevated bladder tumour incidence was due to the increased incidence of a tumour considered to be unique to mice.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Mannitol, carbomer 974P, sodium chloride, tyloxapol, disodium edetate, sodium hydroxide and/or hydrochloric acid (for pH adjustment), purified water and benzalkonium chloride.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

Discard container 4 weeks after opening.

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C.

6.5 NATURE AND CONTENTS OF CONTAINER

BrinzoQuin Eye Drops 1.0% is available in LDPE bottle dispenser. Pack sizes: 1 x 5 mL and 1 x 10 mL.

Not all pack sizes may be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

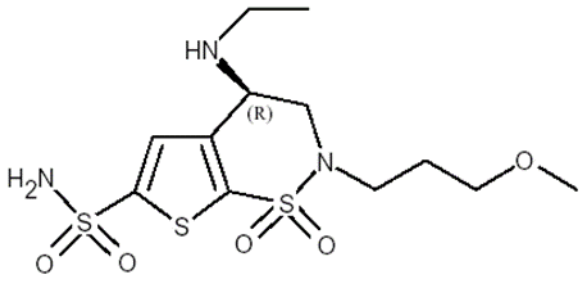
In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 PHYSICOCHEMICAL PROPERTIES

Brinzolamide is presented as white to off-white crystals or powder.

Brinzolamide is very slightly soluble in water at neutral pH.

Chemical structure



Molecular weight: 383.51

Empirical formula: $C_{12}H_{21}N_3O_5S_3$

Chemical name: (R)-4-(Ethylamino)-3,4-dihydro-2-(3-methoxypropyl)-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide-1,1-dioxide

CAS number

138890-62-7

7 MEDICINE SCHEDULE (POISONS STANDARD)

Prescription Only Medicine (Schedule 4)

8 SPONSOR

Novartis Pharmaceuticals Australia Pty Limited
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54 Waterloo Road
Macquarie Park NSW 2113

Telephone 1 800 671 203
Web site: www.novartis.com.au

® = Registered Trademark

9 DATE OF FIRST APPROVAL

20 May 2004

10 DATE OF REVISION

09 November 2023

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
6.5	Delete "DROP-TAINER®"

Internal document code: brq091123i based on CDS dated 05 Nov 2020 and 26 May 2022