NEW ZEALAND DATA SHEET

1. PRODUCT NAME

AZOPT® Eye Drops 1%

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Azopt contains the active ingredient brinzolamide 10 mg in 1 mL (1%).

Excipient with known effect

Benzalkonium chloride 0.1 mg/mL as a preservative.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Eye drops, suspension.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Decrease in intraocular pressure in ocular hypertension and open angle glaucoma.

4.2 Dose and method of administration

Azopt Eye Drops should be shaken well prior to use.

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

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

Concomitant therapy

Azopt has been used concomitantly with other agents e.g. travoprost, latanoprost, timolol (see Section 5.1 Pharmacodynamic properties, Clinical efficacy and safety).

In case of concomitant therapy with more than one topical ophthalmic medicinal product is being used, the medicines 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.

Patients should be advised that instillation of eye drops may cause initial discomfort (see Section 4.8 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 Azopt and to wait fifteen minutes after instillation of the dose before reinsertion.

4.3 Contraindications

Azopt is contraindicated in patients with a known hypersensitivity to brinzolamide, sulfonamides or any of the excipients listed under Section 6.1.

Azopt 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. Azopt 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 sulphonamide derivatives, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), can occur in patients receiving Azopt. At the time of prescription, patients should be advised of the signs and symptoms and monitored closely for skin reactions. Azopt 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 Azopt. The concomitant administration of Azopt and oral carbonic anhydrase inhibitors has not been studied and is not recommended.

Acid-base disturbances have been reported with oral carbonic anhydrase inhibitors. Azopt 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.

Paediatric use

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

Use in the elderly

In clinical studies conducted with Azopt, 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.

Use in hepatic impairment

Azopt has not been studied in patients with hepatic impairment. Caution should, therefore, be exercised if a decision is made to commence therapy with Azopt Eye Drops 1.0% in such patients.

Use in renal impairment

Azopt 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; Azopt is therefore, contraindicated in such patients (See Section 4.3 Contraindications).

Use with contact lenses

Azopt 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 Azopt and wait at least 15 minutes before reinsertion.

4.5 Interaction with other medicines and other forms of interaction

Specific drug interaction studies have not been performed with Azopt. In clinical studies, however, Azopt was 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 Azopt 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 Azopt.

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

4.6 Fertility, pregnancy and lactation

Pregnancy (Category 3)

No studies of the use of ophthalmic brinzolamide have been conducted in pregnant women. Azopt should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus. Refer to Section 5.3 for pre-clinical studies on brinzolamide.

Breast-feeding

It is not known whether brinzolamide is transferred into human milk following topical ocular administration. A risk to the newborns/infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from AZOPT therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.
Studies in animals have shown that following oral administration brinzolamide is excreted in breast milk. Following oral administration of 14C-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.

Fertility

Refer to Section 5.3 for pre-clinical studies on brinzolamide.

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 Undesirable effects).

4.8 Undesirable effects

In well-controlled clinical studies, undesirable effects related to Azopt 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 of 1% or greater), which have been generated from all clinical studies with Azopt, are provided in Table 1 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 the table 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 (%) Figures

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

Adverse Events	Brinz 1.0%	Brinz 1.0% + Tim 0.5%	Dorz 2%	Tim 0.5%	Placebo
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					
Body as a whole					
Headache	1.3	0.5	1.3	0.8	0.9
Respiratory					
Rhinitis	0.2	-	1.0	-	-
Dyspnoea	0.2	-	-	2.0	-
Asthma	-	1.0	-	0.8	-
Special Senses					
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 Azopt 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, irregular heart rate.

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 generalized.

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 drug reaction**
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 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 https://nzphvc.otago.ac.nz/reporting.

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 Azopt may be flushed from the eyes with warm tap water.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764 766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Sensory organ; ophthalmologicals; antiglaucoma preparations and miotics; carbonic anhydrase inhibitors; ATC code: S01EC04.

Mechanism of action

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

Pharmacodynamic effects

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 per fusion. 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 Ki 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 efficacy and safety

In two randomised, double-masked studies of 3 month duration, monotherapy with Azopt 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 Azopt 1.0% three times daily.

Table 3. Average Intraocular Pressure Reduction

% Reduction, Absolute Reduction in mm Hg (n)		
	10 AM	**6 PM**
Study 1		
Azopt 1% 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		
Azopt 1% 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 Azopt 1.0% (n=94) with timolol maleate 0.5% (n=49; both twice daily), the mean absolute change 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 Azopt 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 Azopt 1.0% versus timolol maleate 0.5% on pulmonary function as measured by forced expiratory volume in one second (FEV_1). Within 15 minutes of the instillation of a single drop of timolol maleate 0.5%, statistically significant decreases in mean FEV_1 were observed (compared to both baseline and Azopt 1.0%); these continued for up to 3 hours following instillation. No effect was observed on FEV_1 following the instillation of Azopt.

Two masked, well-controlled studies, each of one-week duration, were designed to compare the comfort of Azopt 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 Azopt 1.0%, as tabulated below.

Table 4. Percent Patients Experiencing No Discomfort (n)

	Azopt 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 Azopt when added concomitantly to prostaglandins (i.e. travoprost and latanoprost). The available data support a lowering of IOP when Azopt 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, Azopt 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 Azopt 1.0% three times daily.

Table 5. Average Intraocular Pressure Reduction

% Reduction, Absolute Reduction in mm Hg (n)		
	9 AM	**11 AM**
Study 3		
Azopt 1% twice daily*	-17.1%, -4.3 (101)	-19.9%, -4.9 (102)
Dorzolamide 2% twice 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 Azopt 1.0% in combination with timolol maleate 0.5% achieved an intraocular pressure reduction of ≥ 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 Azopt 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 Azopt 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-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 that observed orally and unlikely to elicit systemic side effects.

5.3 Preclinical safety data

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.

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.

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.

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 14C-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.

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), benzalkonium chloride 0.1 mg/mL as a preservative and purified water.

6.2 Incompatibilities

Unknown.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store Azopt Eye Drops at temperatures below 25°C.

Contents should be discarded four weeks after opening.

Azopt must be kept out of the sight and reach of children.

6.5 Nature and contents of container

Multi-dose 5 mL LDPE Bottle.

6.6 Special precautions for disposal

No special requirements for disposal.

7. MEDICINE SCHEDULE

Prescription Medicine.

8. SPONSOR

Novartis New Zealand Limited

PO Box 99102

Newmarket

Auckland 1149

New Zealand.

Free Phone: 0800 354 335

® = Registered Trademark

9. DATE OF FIRST APPROVAL

23 November 2000

10. DATE OF REVISION OF THE TEXT

13 June 2023

SUMMARY TABLE OF CHANGES

Section	Summary of Changes
6.5 Nature and contents of container	Delete “Drop-Tainer®” and relocate “5 mL”

Internal document code

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