AUSTRALIAN PRODUCT INFORMATION –

SIMBRINZA® (brinzolamide / brimonidine tartrate) Eye Drops

1 NAME OF THE MEDICINE

Brinzolamide / brimonidine tartrate

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

SIMBRINZA contains brinzolamide 1% (10 mg/mL) and brimonidine tartrate 0.2% (2 mg/mL) as the active ingredients.

Excipient with known effect: benzalkonium chloride.

May contain potential allergen such as benzoates, sulfites and hydroxybenzoates from the manufacturing process.

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

3 PHARMACEUTICAL FORM

Eye drops, suspension.

SIMBRINZA is a white to off-white uniform suspension for multiple-dose topical ophthalmic use. The pH of SIMBRINZA is approximately 6.5.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Decrease of elevated intraocular pressure (IOP) in adult patients with open-angle glaucoma or ocular hypertension for whom monotherapy provides insufficient IOP reduction.

4.2 DOSE AND METHOD OF ADMINISTRATION

Dosage

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

If a dose is missed, treatment should be continued with the next dose as planned. The dose should not exceed one drop in the affected eye(s) twice daily.

When substituting another ophthalmic antiglaucoma agent with SIMBRINZA, the other agent should be discontinued and SIMBRINZA should be started the following day.

SIMBRINZA may be used concomitantly with other topical ophthalmic medicinal products to lower intraocular pressure. If more than one topical ophthalmic medicine is being used, the medicines must be administered at least 5 minutes apart. Eye ointments should be administered last.

Method of administration

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

After the cap is removed, if tamper evident snap collar is loose, this should be removed before using the product.

To prevent contamination of the dropper tip and solution, care must be taken not to touch the eyelids, surrounding areas or other surfaces with the dropper tip of the bottle. Instruct patients to keep the bottle tightly closed when not in use. For individual patient use only.

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

SIMBRINZA may be used while wearing contact lenses with careful monitoring. Patients must be instructed to remove contact lenses prior to application of SIMBRINZA and wait at least 15 minutes before reinsertion. (See Section 4.4 Special warnings and precautions for use, Ocular effects, Corneal Endothelium; Section 4.4 Special warnings and precautions for use, Benzalkonium chloride).

4.3 CONTRAINDICATIONS

A history of hypersensitivity to brinzolamide and other sulphonamides, brimonidine or any other component of the medication.

The following conditions may also contraindicate the use of SIMBRINZA:

- patients receiving monoamine oxidase (MAO) inhibitor therapy
- patients on antidepressants which affect noradrenergic transmission (e.g. tricyclic antidepressants and mianserin)
- severe renal impairment (see Section 4.4 Special warnings and precautions for use, Use in hepatic /renal impairment)
- hyperchloraemic acidosis.

SIMBRINZA is contraindicated in children under 2 years.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Identified precautions

FOR TOPICAL USE ONLY – NOT FOR INJECTION OR ORAL INGESTION

SIMBRINZA should be discontinued at the first appearance of a skin rash or any other sign of hypersensitivity.

Ocular effects

Acute Angle-Closure Glaucoma

SIMBRINZA has not been studied in patients with acute angle-closure glaucoma and its use is not recommended in these patients.

Corneal Endothelium
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) or in patients wearing contact lenses. Carbonic anhydrase inhibitors may affect corneal hydration, which may lead to a corneal decompensation and oedema. Careful monitoring is recommended in patients wearing contact lenses or in patients with compromised corneas (e.g. patients with diabetes mellitus or corneal dystrophies). Risk factors for corneal disease include overuse of preserved eye drops and tear deficiency.

SIMBRINZA may be used while wearing contact lenses with careful monitoring (see below, under Benzalkonium chloride).

Hypersensitivity reactions
Brimonidine tartrate may cause ocular allergic reactions. If allergic reactions are observed, treatment should be discontinued. Delayed ocular hypersensitivity reactions have been reported with brimonidine tartrate, with some reported to be associated with an increase in IOP.

Systemic effects
Hypersensitivity reactions
SIMBRINZA contains brinzolamide, a sulphonamide inhibitor of carbonic anhydrase and, although administered topically, is absorbed systemically. Systemic absorption can be minimized by nasolacrimal occlusion (see section 4.2 Dose and method of administration). The same types of adverse reactions that are attributable to sulphonamides may occur with topical administration. Serious hypersensitivity reactions to sulfonamides have been reported including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), fulminant hepatic necrosis, agranulocytosis, aplastic anemia, and other blood dyscrasias. At the time of prescription, patients should be advised of the signs and symptoms and monitored closely for skin reactions. Sensitization may recur when a sulfonamide is re-administered irrespective of the route of administration. If signs of serious reactions or hypersensitivity occur, the use of this medicinal product should be discontinued immediately and physician contacted.

Cardiac disorders
Following administration of SIMBRINZA, small decreases in blood pressure were observed in some patients. Caution is advised when using drugs such as antihypertensives and/or cardiac glycosides concomitantly with SIMBRINZA or in patients with severe or unstable and uncontrolled cardiovascular disease.

SIMBRINZA should be used with caution in patients with depression, cerebral or coronary insufficiency, Raynaud's phenomenon, orthostatic hypotension or thromboangiitis obliterans due to the brimonidine tartrate component.

Acid/base disturbances
Acid-base disturbances have been reported with oral carbonic anhydrase inhibitors. SIMBRINZA contains brinzolamide, an inhibitor of carbonic anhydrase, and although administered topically, is absorbed systemically. The same types of adverse reactions that are attributable to oral carbonic inhibitors (i.e. acid-base disturbances) may occur with topical administration of SIMBRINZA.

SIMBRINZA should be used with caution in patients with risk of renal impairment because of the possible risk of metabolic acidosis. SIMBRINZA is contraindicated in patients with severe renal impairment.

Mental alertness

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

Concomitant therapy

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

Concomitant use of salicylates (e.g. aspirin) with SIMBRINZA is not recommended especially with high dose therapy (>1 g daily) as this may lead to decreased efficacy of the salicylate, CNS toxicity, metabolic acidosis and other adverse reactions.

Benzalkonium chloride

SIMBRINZA contains benzalkonium chloride which may cause eye irritation and is known to discolour soft contact lenses. Contact with soft contact lenses is to be avoided. Patients must be instructed to remove contact lenses prior to the application of SIMBRINZA and wait 15 minutes after instillation of the dose before reinsertion.

Benzalkonium chloride has also been reported to cause punctate keratopathy and/or toxic ulcerative keratopathy. Close monitoring is required with frequent or prolonged use.

Use in hepatic impairment

No studies have been conducted with SIMBRINZA in patients with hepatic impairment, caution should be exercised in treating such patients.

Use in renal impairment

No studies have been conducted with SIMBRINZA in patients with renal impairment, caution should be exercised in treating such patients.

SIMBRINZA has not been studied in patients with severe renal impairment (creatinine clearance <30 mL/min) or in patients with hyperchloraemic acidosis. Since brinzolamide and its main metabolite are excreted predominantly by the kidney, SIMBRINZA is therefore contraindicated in patients with severe renal impairment.

Use in the elderly

There are no modifications to the recommended dosing regimen for elderly patients.

Paediatric use

The safety and efficacy of SIMBRINZA in children and adolescents aged 2 to 17 years has not been established and its use is not recommended in children or adolescents because of the potential for CNS depression from brimonidine tartrate component (see section 4.9 Overdose).

Contraindicated in children under 2 years of age (see section 4.3 Contraindications).

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

No drug interaction studies have been performed with SIMBRINZA.

SIMBRINZA is contraindicated in patients receiving monoamine oxidase inhibitors and patients on antidepressants which affect noradrenergic transmission (e.g. tricyclic antidepressants and mianserin).

Specific drug interaction studies have not been conducted with SIMBRINZA, the possibility of an additive or potentiating effect with CNS depressants (alcohol, barbiturates, opiates, sedatives or anaesthetics) should be considered.

No data on the level of circulating catecholamines after SIMBRINZA administration are available. Caution, however, is advised in patients taking medication which can affect the metabolism and uptake of circulating amines (e.g. chlorpromazine, methylphenidate, reserpine).

The possibility of an additive or potentiating effect with CNS depressants (e.g. alcohol, barbiturates, opiates, sedatives or anaesthetics) should be considered.

Alpha adrenergic agonists (e.g. brimonidine tartrate), as a class, may reduce pulse and blood pressure. Following administration of SIMBRINZA, small decreases in blood pressure were observed in some patients. Caution is advised when using drugs such as antihypertensives and/or cardiac glycosides concomitantly with SIMBRINZA.

Caution is advised when initiating (or changing the dose of) a concomitant systemic agent (irrespective of pharmaceutical form) which may interact with α-adrenergic agonists or interfere with their activity, i.e. agonists or antagonists of the adrenergic receptor (e.g. isoprenaline, prazosin).

Caution is advised in patients taking tricyclic antidepressants as these agents may blunt the ocular hypotensive response.

Brinzolamide, a component of SIMBRINZA, is a carbonic anhydrase inhibitor and, although administered topically, is absorbed systemically. Acid-base disturbances have been reported with oral carbonic anhydrase inhibitors. The potential for interactions (e.g. nonsteroidal anti-inflammatory drugs (NSAIDs) and salicylates) must be considered in patients receiving SIMBRINZA.

There is a potential for an additive effect on the known systemic effects of carbonic anhydrase inhibition in patients treated with an oral carbonic anhydrase inhibitor and topical brinzolamide. The

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

Concomitant use of salicylates (e.g., aspirin) with SIMBRINZA is not recommended especially with high dose therapy (>1 gm daily) as this may lead to decreased efficacy of the salicylate, CNS toxicity, metabolic acidosis and other adverse reactions.

The cytochrome P-450 isozymes responsible for metabolism of brinzolamide include CYP3A4 (main), CYP2A6, CYP2B6, CYP2C8 and CYP2C9. It is expected that inhibitors of CYP3A4 such as ketoconazole, itraconazole, clotrimazole ritonavir and troleandomycin will inhibit the metabolism of brinzolamide by CYP3A4. Caution is advised if CYP3A4 inhibitors are given concomitantly. However, accumulation of brinzolamide is unlikely as renal elimination is the major route. Brinzolamide is not an inhibitor of cytochrome P-450 isozymes.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

There are no human data on the effects of SIMBRINZA on male or female fertility. No animal fertility study has been conducted with brinzolamide and brimonidine in combination. Studies with the individual active components in rats, in which animals were treated orally with brinzolamide up to 18 mg/kg/day or with brimonidine at up to 0.66 mg/kg/day, showed no adverse effects on male or female fertility.

Use in pregnancy – Category B3

No studies have been conducted with SIMBRINZA in pregnant women, and no animal studies have been conducted with the combined components to evaluate effects on reproduction. There are also no adequate and well controlled studies using brinzolamide and brimonidine individually in pregnant women. Studies in animals with brinzolamide and brimonidine individually have shown reproductive toxicity following systemic administration. SIMBRINZA should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

Brinzolamide

Developmental toxicity studies with brinzolamide in rabbits at oral doses up to 6 mg/kg/day produced maternal toxicity at 6 mg/kg/day and a significant increase in the number of foetal variations, e.g. accessory skull bones; at 1 and 6 mg/kg/day, the incidence was only slightly higher than seen historically. In rats, statistically significant decreased bodyweights 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. Exposure levels are much lower following topical administration of brinzolamide. In both rats and rabbits, brinzolamide was not teratogenic.

Brimonidine

Brimonidine was shown to cross the placenta and enter the foetal circulation in rats. In pregnant rats, brimonidine was associated with maternotoxicity and increased early resorptions/post-implantation losses and decreased pup viability and bodyweights at exposures (based on AUC) of 180 times greater than expected exposures in humans treated therapeutically. The drug was also maternotoxic in rabbits

and caused abortions at exposures about 12 times greater than those expected in humans. In both rats and rabbits, brimonidine was not teratogenic.

Use in lactation

It is not known whether brinzolamide and brimonidine is transferred in human milk following topical ocular administration.

Studies in animals have shown that following oral administration, brinzolamide and brimonidine are 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 prenatal and postnatal study in which rats were given brinzolamide by oral gavage at doses up to 15 mg/kg/day. With brimonidine in lactating rats, levels of the drug in milk were up to 12 times higher than those in maternal plasma; and in a peri- and postnatal study in rats, brimonidine was associated with decreased pup viability and pup weights during lactation at maternal plasma exposures of about 55 times greater than those expected in humans.

Because of the potential for serious adverse reactions in breastfed infants from brinzolamide and brimonidine, a decision should be made whether to discontinue breastfeeding or to discontinue SIMBRINZA, taking into account the benefit of breastfeeding for the child and the benefit of therapy for the mother.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

As with any eye drops, temporary blurred vision or other visual disturbances may affect the ability to drive or use machines. If blurred vision occurs at instillation, the patient must wait until the vision clears before driving or using machinery. Carbonic anhydrase inhibitors may impair the ability to perform tasks requiring mental alertness and/or physical coordination.

The brimonidine component of SIMBRINZA may cause fatigue and/or drowsiness, which may impair the ability to drive or operate machinery.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

SIMBRINZA contains brinzolamide which 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 attributable to oral carbonic anhydrase inhibitors may occur with topical administration of SIMBRINZA.

Adverse reactions commonly associated with the brimonidine component of SIMBRINZA include the development of ocular allergic type reactions, fatigue and/or drowsiness, and dry mouth. The use of brimonidine has been associated with minimal decreases in blood pressure. Some patients who were dosed with SIMBRINZA experienced decreases in blood pressure similar to those observed with the use of brimonidine as monotherapy.

In clinical trials involving SIMBRINZA dosed twice-daily, the most common adverse reactions were ocular hyperaemia and ocular allergic type reactions occurring in approximately 6-7% of patients. The

safety profile of SIMBRINZA was similar to that of the individual components (brinzolamide 10 mg/mL and brimonidine 2 mg/mL) and did not result in additional risk to patients relative to the known risks of the individual components.

The following adverse reactions were assessed to be treatment-related. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

The adverse reactions are listed by MedDRA system organ class and frequency using the following 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); very rare (<1/10,000) and not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in the order of decreasing clinical importance.

Table 1. Adverse reactions in clinical trials

System Organ Classification	Adverse reactions
Infections and infestations	Uncommon: nasopharyngitis[2], pharyngitis[2], sinusitis[2] Not known: rhinitis[2]
Blood and lymphatic system disorders	Uncommon: red blood cell decreased[2], blood chloride increased[2]
Immune system disorders	Uncommon: hypersensitivity[3]
Psychiatric disorders	Uncommon: apathy[2], depression[2,3], depressed mood[2], insomnia[1], libido decreased[2], nightmare[2], nervousness[2]
Nervous system disorders	Common: somnolence[1], dizziness[3], dysgeusia[1] Uncommon: headache[1], motor dysfunction[2], amnesia[2], memory impairment[2], paraesthesia[2] Very rare: syncope[3] Not known: tremor[2], hypoaesthesia[2], ageusia[2]
Eye disorders	Common: eye allergy[1], keratitis[1], eye pain[1], ocular discomfort[1], blurred vision[1], abnormal vision[3], ocular hyperaemia[1], conjunctival blanching[3] Uncommon: corneal erosion[1], corneal oedema[2], blepharitis[1], corneal deposits (keratic precipitates) [1], conjunctival disorder (papillae) [1], photophobia[1], photopsia[2], eye swelling[2], eyelid oedema[1], conjunctival oedema[1], dry eye[1], eye discharge[1], visual acuity reduced[2], lacrimation increased[1], pterygium[2], erythema of eyelid[1], meibomianitis[2], diplopia[2], glare[2], hypoaesthsia eye[2], scleral pigmentation[2], subconjunctival cyst[2], abnormal sensation in eye[1], asthenopia[1] Very rare: uveitis[3], miosis[3] Not known: visual disturbances[2], madarosis[2]

System Organ Classification	Adverse reactions
Ear and labyrinth disorders	Uncommon: vertigo[1], tinnitus[2]
Cardiac disorders	Uncommon: cardio-respiratory distress[2], angina pectoris[2], arrhythmia[3], palpitations[2,3], heart rate irregular[2], bradycardia[2,3], tachycardia[3]
Vascular disorders	Uncommon: hypotension[1] Very rare: hypertension[3]
Respiratory, thoracic and mediastinal disorders	Uncommon: dyspnoea[2], bronchial hyperactivity[2], pharyngolaryngeal pain[2], dry throat[1], cough[2], epistaxis[2], upper respiratory tract congestion[2], nasal congestion[1], rhinorrhea[2], throat irritation[2], nasal dryness[1], postnasal drip[1], sneezing[2] Not known: asthma[2]
Gastrointestinal disorders	Common: dry mouth[1] Uncommon: dyspepsia[1], oesophagitis[2], abdominal discomfort[1], diarrhoea[2], vomiting[2], nausea[2], frequent bowel movements[2], flatulence[2], hypoaesthesia oral[2], paraesthesia oral[1]
Hepatobiliary disorders	Not known: liver function test abnormal[2]
Skin and subcutaneous tissue disorders	Uncommon: dermatitis contact[1], urticaria[2], rash[2], rash maculo- papular[2], pruritus generalized[2], alopecia[2], skin tightness[2] Not known: face oedema[3], dermatitis[2,3], erythema[2,3]
Musculoskeletal and connective tissue disorders	Uncommon: back pain[2], muscle spasms[2], myalgia[2] Not known: arthralgia[2], pain in extremity[2]
Renal and urinary disorders	Uncommon: renal pain[2] Not known: pollakiuria[2]
Reproductive system and breast disorders	Uncommon: erectile dysfunction[2]
General disorders and administration site conditions	Uncommon: pain[2], chest discomfort[2], feeling abnormal[2], feeling jittery[2], irritability[2], medication residue[1] Not known: chest pain[2], peripheral oedema[2,3]

[1] adverse reaction observed with SIMBRINZA

[2] additional adverse reaction observed with brinzolamide monotherapy

[3] additional adverse reaction observed with brimonidine monotherapy

Adverse drug reactions from spontaneous reports and literature cases (frequency not known)

The following adverse drug reactions have been derived from post-marketing experience with SIMBRINZA via spontaneous case reports and literature cases. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency which is therefore categorized as not known. Adverse drug reactions are listed according to system organ classes in MedDRA. Within each system organ class, ADRs are presented in order of decreasing seriousness.

Table 2. Adverse drug reactions from spontaneous reports and literature (frequency unknown)

System organ classification	Adverse drug reaction
Skin and subcutaneous tissue disorders	Stevens-Johnson syndrome (SJS), Toxic epidermal necrolysis (TEN)

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

A topical overdose of SIMBRINZA may be flushed from the eye(s) with warm tap water.

If an overdose with SIMBRINZA occurs, treatment should be symptomatic and supportive. The patient's airway should be supported.

Due to brinzolamide, electrolyte imbalance, development of an acidotic state and possibly central nervous system effects may occur. Serum electrolyte levels (particularly potassium) and blood pH levels should be monitored.

Nasolacrimal occlusion and gently closing the eyelid after instillation may reduce the systemic absorption of eye drops and result in a decrease in systemic adverse reactions (See Section 4.2 Dose and method of administration).

There is very limited information regarding accidental ingestion with the brimonidine component of SIMBRINZA in adults. The only adverse event reported to date was hypotension. It was reported that the hypotensive episode was followed by rebound hypertension. Treatment of oral overdose includes supportive and symptomatic therapy; patient's airway should be maintained.

Oral overdoses of other alpha-2-agonists have been reported to cause symptoms such as hypotension, asthenia, vomiting, lethargy, sedation, bradycardia, arrhythmias, miosis, apnoea, hypotonia, hypothermia, respiratory depression and seizure.

Paediatric population

SIMBRINZA is for use in adults, 18 years of age or older. Serious adverse effects following inadvertent ingestion with the brimonidine tartrate component of SIMBRINZA by paediatric subjects have been reported. The subjects experienced symptoms of CNS depression, typically temporary coma or low level of consciousness, lethargy, somnolence, hypotonia, bradycardia, hypothermia, pallor, respiratory depression and apnoea, and required admission to intensive care with intubation if indicated.

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

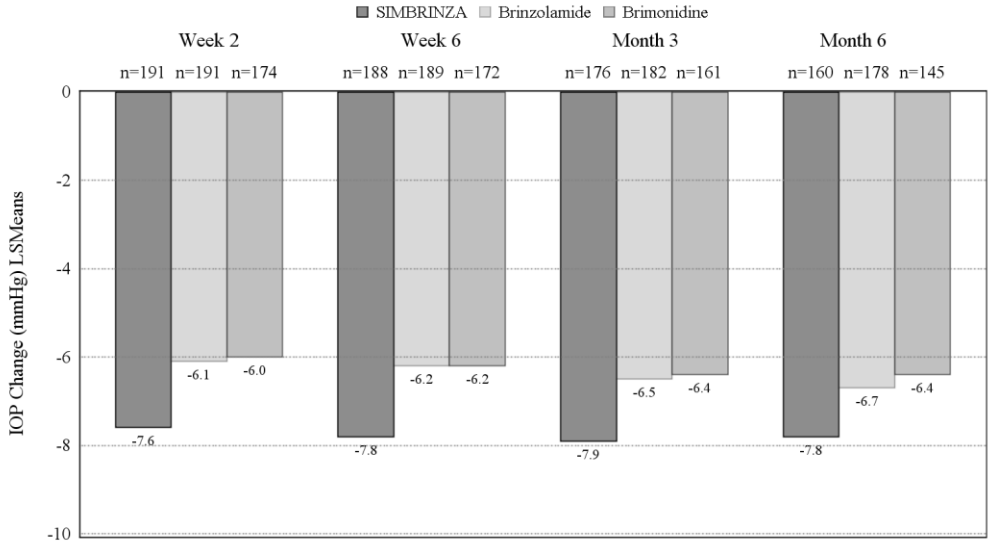
SIMBRINZA contains two active substances: brinzolamide and brimonidine tartrate. These two components lower intraocular pressure (IOP) by suppressing the formation of aqueous humour from the ciliary process in the eye. Although both brinzolamide and brimonidine lower IOP by suppressing aqueous humour formation, their mechanisms of action are different.

Brinzolamide acts by inhibiting the enzyme carbonic anhydrase in the ciliary epithelium that reduces the formation of bicarbonate ions with subsequent reduction in sodium and fluid transport across the ciliary epithelium, resulting in decreased aqueous humour formation. Brimonidine, an alpha-2 adrenergic agonist, inhibits the enzyme adenylate cyclase and suppresses the cAMP-dependent formation of aqueous humour. Additionally, brimonidine causes an increase in uveoscleral outflow.

Clinical trials

A 6-month, controlled, contribution of elements clinical study was performed enrolling 560 patients with open-angle glaucoma (including pseudoexfoliation or pigment dispersion component) and/or ocular hypertension who, in the investigator's opinion, were insufficiently controlled on monotherapy or already on multiple IOP-lowering medications, and who had baseline mean diurnal IOP of 26 mmHg. In this study, the mean diurnal IOP-lowering effect of SIMBRINZA, dosed twice daily, was 8 mmHg, with IOP diurnal reductions 1 to 2 mmHg greater than that of brinzolamide 10 mg/mL and 1 to 2 mmHg greater than brimonidine 2 mg/mL dosed twice daily. Statistically superior reductions in the mean diurnal IOP were observed with SIMBRINZA compared to brinzolamide or brimonidine at all visits throughout the study (Figure 1).

Figure 1 Mean[a] Diurnal (9 AM, +2 Hrs, +7 Hrs) IOP Change from Baseline (mmHg) Contribution of Elements Study



[a] Least squares means derived from a statistical model that accounts for study site, 9 AM baseline IOP stratum and correlated IOP measurements within patient.

All treatment differences (SIMBRINZA versus individual components) were statistically significant with p=0.0001 or less.

Mean IOP reductions from baseline at each time point at each visit were greater with SIMBRINZA (6 to 9 mmHg) than monotherapy with either brinzolamide (5 to 7 mmHg) or brimonidine (4 to 7 mmHg). Mean percent IOP reductions from baseline with SIMBRINZA ranged from 23 to 34%. The percentages of patients with an IOP measurement less than 18 mmHg were greater in the SIMBRINZA group than in the brinzolamide group at 11 of 12 assessments through Month 6 and were greater in the SIMBRINZA group than in the brimonidine group at all 12 assessments through Month 6. At the + 2 h time point (the time corresponding to the morning efficacy peak) for the primary efficacy visit at Month 3, the percentage of patients with an IOP less than 18 mmHg was 68.8% in the SIMBRINZA group, 42.3% in the brinzolamide group and 44.0% in the brimonidine group.

In a 6-month, controlled, non-inferiority clinical study enrolling 890 patients with open-angle glaucoma (including pseudoexfoliation or pigment dispersion component) and/or ocular hypertension who, in the investigator's opinion, were insufficiently controlled on monotherapy or already on multiple IOP-lowering medications, and who had baseline mean diurnal IOP of 26 to 27 mmHg, the mean diurnal IOP-lowering effect of SIMBRINZA dosed twice daily was 8 to 9 mmHg. The non-inferiority of SIMBRINZA compared to brinzolamide 10 mg/mL + brimonidine 2 mg/mL dosed concomitantly with respect to mean diurnal IOP reduction from baseline was demonstrated at all visits throughout the study (Table 3).

Table 3 Comparison of Mean Diurnal IOP (mmHg) Change from Baseline Non-inferiority Study

Visit	Change in IOP SIMBRINZA® Mean[a] (mmHg)	Change in IOP Brinzolamide + Brimonidine Mean[a] (mmHg)	Difference Mean[a] (95% CI)
Week 2	-8.4 (n=394)	-8.4 (n=384)	-0.0 (-0.4, 0.3)
Week 6	-8.5 (n=384)	-8.4 (n=377)	-0.1 (-0.4, 0.2)
Month 3	-8.5 (n=384)	-8.3 (n=373)	-0.1 (-0.5, 0.2)
Month 6	-8.1 (n=346)	-8.2 (n=330)	0.1 (-0.3, 0.4)

[a] Least squares means derived from a statistical model that accounts for study site, 9 AM baseline IOP stratum and correlated IOP measurements within patient

Mean IOP reductions from baseline at each time point at each visit with SIMBRINZA or the individual components administered concomitantly were similar (7 to 10 mmHg). Mean percent IOP reductions from baseline with SIMBRINZA ranged from 25% to 37%. The percentages of patients with an IOP measurement less than 18 mmHg were similar across study visits for the same time point through Month 6 in the SIMBRINZA and brinzolamide + brimonidine groups. At the + 2 hour time point (the time corresponding to the morning efficacy peak) for the primary efficacy visit at Month 3, the percentage of patients with an IOP less than 18 mmHg was 71.6% in both study groups.

Mean diurnal IOP (mmHg) for SIMBRINZA compared to brinzolamide or brimonidine at Month 3 and Month 6 is provided in Table 4. Mean IOP (mmHg) for SIMBRINZA compared to brinzolamide or brimonidine at Month 3 and Month 6 at all-time points is provided in Table 5.

Table 4 Comparison of Mean Diurnal IOP (mmHg) Contribution of Elements Study

Visit	Diurnal IOP SIMBRINZA® Mean[a] (mmHg)	Diurnal IOP Brinzolamide Mean[a] (mmHg)	Difference Mean[a] (95% CI)
Month 3	18.0 (n=176)	19.4 (n=182)	-1.4 (-1.9, -0.8)
Month 6	18.1 (n=160)	19.2 (n=178)	-1.1 (-1.6, -0.5)
Visit	Diurnal IOP SIMBRINZA® Mean[a] (mmHg)	Diurnal IOP Brimonidine Mean[a] (mmHg)	Difference Mean[a] (95% CI)
Month 3	18.0 (n=176)	19.4 (n=161)	-1.4 (-2.0, -0.9)
Month 6	18.1 (n=160)	19.4 (n=145)	-1.3 (-1.9, -0.8)

[a] Least squares means derived from a statistical model that accounts for study site, 9 AM baseline IOP stratum and correlated IOP measurements within patient. All treatment differences (SIMBRINZA versus individual components) were statistically significant with p=0.0002 or less.

Table 5 Comparison of Mean IOP (mmHg) Contribution of Elements Study

Visit	Time point	SIMBRINZA® IOP Mean[a] (mmHg)	Brinzolamide IOP Mean[a] (mmHg)	Difference Mean[a] (95% CI)
Month 3	9 AM	20.2 (n=176)	21.0 (n=182)	-0.8 (-1.5, -0.1)
	+2 Hrs	17.3 (n=173)	19.6 (n=182)	-2.3 (-3.0, -1.7)
	+7 Hrs	18.1 (n=172)	19.4 (n=180)	-1.3 (-2.0, -0.6)
Month 6	9 AM	20.3 (n=160)	21.0 (n=178)	-0.7 (-1.4, -0.0)
	+2 Hrs	17.5 (n=160)	19.5 (n=178)	-2.0 (-2.7, -1.3)
	+7 Hrs	18.3 (n=160)	19.1 (n=178)	-0.8 (-1.5, -0.1)
Visit	Time point	SIMBRINZA® IOP Mean[a] (mmHg)	Brimonidine IOP Mean[a] (mmHg)	Difference Mean[a] (95% CI)
Month 3	9 AM	20.2 (n=176)	21.6 (n=161)	-1.4 (-2.1, -0.8)
	+2 Hrs	17.3 (n=173)	18.7 (n=159)	-1.4 (-2.1, -0.7)
	+7 Hrs	18.1 (n=172)	20.0 (n=159)	-1.9 (-2.6, -1.2)
Month 6	9 AM	20.3 (n=160)	21.5 (n=145)	-1.2 (-2.0, -0.5)
	+2 Hrs	17.5 (n=160)	19.2 (n=145)	-1.7 (-2.4, -1.0)
	+7 Hrs	18.3 (n=160)	19.7 (n=144)	-1.4 (-2.1, -0.7)

[a] Least squares means derived from a statistical model that accounts for study site, 9 AM baseline IOP stratum and correlated IOP measurements within patient. All treatment differences (SIMBRINZA versus individual components) were statistically significant with p=0.0386 or less.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Brinzolamide is absorbed through the cornea following topical ocular administration. The drug is also absorbed into the systemic circulation where it binds strongly to carbonic anhydrase in red blood cells. Plasma drug concentrations are very low. Whole blood elimination half-life is prolonged (>100 days) in humans due to red blood cell carbonic anhydrase binding.

Brimonidine is rapidly absorbed into the eye following topical administration. In rabbits, maximum ocular concentrations were achieved in less than one hour in most cases. Maximum human plasma concentrations are <1 ng/mL and achieved within <1 hour. Plasma drug levels decline with a half-life of approximately 2-3 hours. No accumulation occurs during chronic administration.

In a topical ocular clinical study comparing the systemic pharmacokinetics of SIMBRINZA to brinzolamide and brimonidine administered individually, the steady-state whole blood brinzolamide and N-desethylbrinzolamide pharmacokinetics were similar between the combination product and

brinzolamide administered alone. Likewise, the steady-state plasma pharmacokinetics of brimonidine from the combination was similar to that observed for brimonidine administered alone.

Distribution

Studies in rabbits showed that maximum ocular brinzolamide concentrations following topical administration are in the anterior tissues such as cornea, conjunctiva, aqueous humour and iris-ciliary body. Retention in ocular tissues is prolonged due to binding to carbonic anhydrase. Brinzolamide is moderately bound (about 60%) to human plasma proteins.

Brimonidine exhibits affinity for pigmented ocular tissues, particularly iris-ciliary body, due to its known melanin binding properties. However, clinical and non-clinical safety data show the drug to be well-tolerated and safe during chronic administration.

Metabolism

Brinzolamide is metabolised by hepatic cytochrome P450 isozymes, specifically CYP3A4, CYP2A6, CYP2B6, CYP2C8 and CYP2C9. The primary metabolite is N-desethylbrinzolamide, followed by the N-desmethoxypropyl and O-desmethyl metabolites, as well as an N-propionic acid analogue formed by oxidation of the N-propyl side chain of O-desmethyl brinzolamide. Brimonidine is extensively metabolised by hepatic aldehyde oxidase with formation of 2-oxobrimonidine, 3-oxobrimonidine and 2,3-dioxobrimonidine being the major metabolites. Oxidative cleavage of the imidazoline ring to 5-bromo-6-guanidinoquinoxaline is also observed.

Excretion

Brinzolamide is primarily eliminated in urine as unchanged drug. In humans, urinary brinzolamide and N-desethylbrinzolamide accounted for about 60% and 6% of the dose, respectively. Data in rats showed some biliary excretion (about 20%), primarily as metabolites.

Brimonidine is primarily eliminated in the urine as metabolites. In humans, approximately 87% of the radioactivity following an orally-administered radioactive dose was eliminated within 120 hours, with 74% found in the urine.

The steady-state systemic pharmacokinetics of brinzolamide and brimonidine were assessed in volunteers topically dosed twice daily (BID) or three times a day (TID) with SIMBRINZA and the results for BID dosing are summarised in Tables 6 and 7, below. Red blood cell (RBC) concentrations of brinzolamide and its N-desethyl metabolite in pre-dose trough samples were similar between SIMBRINZA and brinzolamide administered alone for both dosing regimens. Similarly, brimonidine plasma pharmacokinetic parameters were similar between SIMBRINZA and brimonidine tartrate 0.2% for both dosing regimens.

Table 6 Least Squares Mean RBC Concentrations (µM) of Brinzolamide and N-Desethyl Brinzolamide Following 107 Days of Topical Ocular Administration of SIMBRINZA or Brinzolamide 1%

Regimen	Analyte	SIMBRINZA	Brinzolamide 1%	Least Squares Means Ratio	Lower 90% Confidence Interval	Uper 90% Confidence Interval
Twice daily (BID)	Brinzolamide	14.2	11.5	1.24	0.996	1.54
	N-Desethyl Brinzolamide	1.56	1.44	1.08	0.772	1.51

Table 7 Brimonidine Mean (Minimum to Maximum) Plasma Pharmacokinetic Parameters Following 21 Days of Topical Ocular Administration of SIMBRINZA or Brimonidine Tartrate 0.2%

Parameter	SIMBRINZA twice daily (BID)	Brimonidine Tartrate 0.2% twice daily (BID)
N	24	24
C_{max} (ng/mL)	0.0724 (0.0234 – 0.179)	0.0639 (0.0279 – 0.114)
T_{max} (hours)	0.50 (0.25 – 1.00)	0.75 (0.25 – 2.00)
$AUC_{0\text{-}inf}$ (ng*hr/mL)	0.196 (0.0580 – 0.408)	0.243 (0.0985 – 0.457)
T1/2 (hours)	2.57 (1.37 – 4.69)	2.38 (1.75 – 3.99)

Linearity/non-linearity

Brinzolamide pharmacokinetics are inherently non-linear due to saturable binding to carbonic anhydrase in whole blood and various tissues. Steady-state exposure does not increase in a dose-proportional manner.

In contrast, brimonidine exhibits linear pharmacokinetics over the clinically therapeutic dose range.

Pharmacokinetic/pharmacodynamic relationship(s)

SIMBRINZA is intended for local action within the eye. Assessment of human ocular exposure at efficacious doses is not feasible. The pharmacokinetic/pharmacodynamic relationship in humans for IOP-lowering has not been established.

Other special populations

Studies to determine the effects of age, race and renal or hepatic impairment have not been conducted with the brinzolamide/brimonidine fixed combination. A study of brinzolamide in Japanese versus non-Japanese subjects showed similar systemic pharmacokinetics between the two groups. In a study of brinzolamide in subjects with renal impairment, a 1.6- to 2.8-fold increase in the systemic exposure to brinzolamide and N-desethylbrinzolamide between normal and moderately renally-impaired subjects was demonstrated. This increase in steady-state red blood cell concentrations of drug-related material did not inhibit red blood cell carbonic anhydrase activity to levels that are associated with systemic side effects. However, the combination product is not recommended for patients with severe renal impairment (creatinine clearance <30 mL/minute).

The C_{max}, AUC and elimination half-life of brimonidine are similar in elderly (>65 years of age) subjects compared to young adults. The effects of renal and hepatic impairment on the systemic pharmacokinetics of brimonidine have not been evaluated. Given the low systemic exposure to brimonidine following topical ocular administration, it is expected that changes in plasma exposure would not be clinically relevant.

Paediatric population

The systemic pharmacokinetics of brinzolamide and brimonidine, alone or in combination, in paediatric patients have not been studied.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Brinzolamide did not display mutagenic potential in bacteria (Ames test) or produce chromosomal damage *in vivo* (mouse micronucleus test). Brinzolamide did induce forward mutations in the mouse lymphoma assay in vitro in the presence, but not in the absence, of metabolic activation. Brinzolamide was negative in a sister chromatid exchange assay in mice.

Brimonidine tartrate was not genotoxic in assays for chromosomal damage (Chinese hamster cells *in vitro*, *in vivo* bone marrow cytogenetic assay and a dominant lethal assay). In assays for gene mutations in *S. typhimurium* and *E. coli*, brimonidine gave a positive response in one *S. typhimurium* strain without metabolic activation; other strains gave negative results.

Carcinogenicity

No carcinogenicity studies have been conducted with the combined components of SIMBRINZA.

Brinzolamide

A 2-year bioassay, in which rats were treated with brinzolamide by oral gavage at doses up to 8 mg/kg/day, revealed no evidence of a carcinogenic effect. A similar study conducted in mice, involving oral dosing at 0, 1, 3 or 10 mg/kg/day for 2 years, revealed a statistically significant increase in urinary bladder tumours in females at 10 mg/kg/day, and dose-related proliferative changes in the urinary bladder in females at all dose levels and among males at 10 mg/kg/day. The elevated bladder tumour incidence was considered to be unique to mice.

Brimonidine

No compound-related carcinogenic effects were observed in 21 month and 2 year studies in mice and rats given oral doses of 2.5 and 1 mg/kg/day respectively as the free base. Plasma concentrations of brimonidine in mice and rats in the high-dose groups were ≥60 times greater than those expected in humans dosed therapeutically.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Propylene glycol, carbomer 974P, boric acid, mannitol, sodium chloride, tyloxapol, sodium hydroxide and/or hydrochloric acid (to adjust pH), purified water and benzalkonium chloride (0.03 mg/mL) as preservative.

6.2 INCOMPATIBILITIES

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

6.3 SHELF LIFE

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

SIMBRINZA should be stored below 25°C. Discard 4 weeks after opening. SIMBRINZA must be kept out of sight and reach of children.

6.5 NATURE AND CONTENTS OF CONTAINER

SIMBRINZA is supplied in 8 mL round opaque low density polyethylene (LDPE) bottles with a LDPE dispensing plug and white polypropylene screw cap containing 5 mL suspension.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

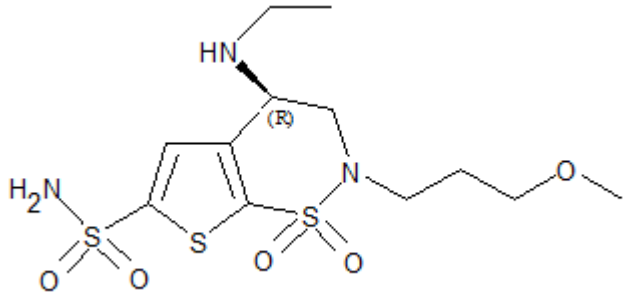
6.7 PHYSICOCHEMICAL PROPERTIES

Brinzolamide is a white to off-white, crystalline powder which is very slightly soluble in water at neutral pH.

Brimonidine tartrate is an off-white, pale yellow to pale pink powder and is water soluble (34 mg/mL). In solution, brimonidine tartrate has a clear, greenish-yellow colour.

Chemical structure

The chemical structure of each active ingredient is represented below:

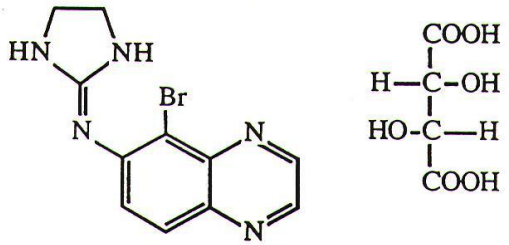


Brinzolamide

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

Molecular weight: 383.51

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



Brimonidine tartrate

Empirical formula: $C_{11}H_{10}BrN_5 \bullet C_4H_6O_6$

Molecular weight: 442.24 as the tartrate salt

Chemical name: 5-bromo-6-(2-imidazolidinyl ideneamino) quinoxaline L-tartrate

CAS number

Brinzolamide: 138890-62-7

Brimonidine tartrate: 79570-19-7

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4, Prescription Only Medicine.

SPONSOR

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8 DATE OF FIRST APPROVAL

20 November 2014

9 DATE OF REVISION

09 November 2023

9.1 SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
6.5	Editorial revision to delete “Drop-tainer®”

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