NEW ZEALAND DATA SHEET

1. PRODUCT NAME

SIMBRINZA® (brinzolamide 1% and brimonidine tartrate 0.2%) Eye Drops.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL of Simbrinza contains a combination of brinzolamide 10 mg in 1 mL and brimonidine tartrate 2 mg in 1 mL.

Excipient with known effect

Benzalkonium chloride 0.03 mg in 1 mL as preservative.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Eye drop suspension.

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

The recommended dosage is one drop of Simbrinza in the conjunctival sac of the affected eye(s) twice daily. Shake the bottle well before use.

Nasolacrimal occlusion and gently closing the eyelid after instillation are recommended. This may reduce the systemic absorption of eye drops and result in a decrease in systemic adverse reactions.

If more than one topical ophthalmic medicine is being used, the medicines must be administered at least 5 minutes apart.

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.

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.

4.3 Contraindications

A history of hypersensitivity to brinzolamide and other sulphonamides, brimonidine or any other component of the medication listed under Section 6.1.

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 Section 4.4 see Hepatic / Renal Impairment.
- hyperchloraemic acidosis.

Simbrinza is not recommended for use in neonates and infants under the age of 2 years.

4.4 Special warnings and precautions for use

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

Simbrinza has not been studied in patients with narrow-angle glaucoma and its use is not recommended in these patients.

The possible role of brinzolamide on corneal endothelial function has not been investigated in patients with compromised corneas (particularly in patients with low endothelial cell count). Specifically, patients wearing contact lenses have not been studied and careful monitoring of these patients when using brinzolamide is recommended, since carbonic anhydrase inhibitors may affect corneal hydration and wearing contact lenses might increase the risk for the cornea. Careful monitoring of patients with compromised corneas, such as patients with diabetes mellitus or corneal dystrophies, is recommended. Simbrinza may be used while wearing contact lenses with careful monitoring (see below under Benzalkonium chloride).

Systemic effects

Simbrinza contains brinzolamide, a sulphonamide inhibitor of carbonic anhydrase and, although administered topically, is absorbed systemically. The same types of adverse reactions that are attributable to sulphonamides may occur with topical 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.

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.

Use 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.

Hepatic / Renal Impairment

No studies have been conducted with Simbrinza in patients with hepatic or renal impairment. 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.

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.

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 gm 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.

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.

Use in the elderly

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

4.5 Interaction with other medicines and other forms of interaction

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, and reserpine).

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 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

Pregnancy

Category C

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. Studies in animals with brinzolamide have shown reproductive toxicity following systemic administration.

Simbrinza is not recommended during pregnancy and in women of child bearing potential not using contraception. Simbrinza should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

Reproductive studies in animals with brinzolamide and brimonidine are included in Section 5.3: Pre-clinical safety data.

Breast-feeding

It is unknown whether topical Simbrinza is excreted in human milk. It is not known whether brinzolamide and brimonidine are excreted in human milk following topical ocular administration.

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 importance of the drug to the mother.

Studies in animals with brinzolamide and brimonidine are included in Section 5.3: Pre-clinical safety data**.**

Fertility

There are no human data on the effects of Simbrinza on male or female fertility.

Studies in animals with brinzolamide and brimonidine are included in Section 5.3: Pre-clinical safety data**.**

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 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.

Psychiatric disorders

Uncommon (≥0.1% to <1%): insomnia.

Nervous system disorders

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

Uncommon (≥0.1% to <1%): headache.

Eye disorders

Common (≥1% to <10%): eye allergy, keratitis, eye pain, ocular discomfort, blurred vision, ocular hyperaemia.

Uncommon (≥0.1% to <1%): corneal erosion, blepharitis, corneal deposits (keratic precipitates), conjunctival disorder (papillae), photophobia, eyelid oedema, conjunctival oedema, dry eye, eye discharge, lacrimation increased, erythema of eyelid, abnormal sensation in eye, asthenopia.

Ear and labyrinth disorders

Uncommon (≥0.1% to <1%): vertigo.

Vascular disorders

Uncommon (≥0.1% to <1%): hypotension.

Respiratory, thoracic and mediastinal disorders

Uncommon (≥0.1% to <1%): dry throat, nasal congestion, nasal dryness, postnasal drip.

Gastrointestinal disorders

Common (≥1% to <10%): dry mouth.

Uncommon (≥0.1% to <1%): dyspepsia, abdominal discomfort, paraesthesia oral.

Skin and subcutaneous tissue disorders

Uncommon (≥0.1% to <1%): dermatitis contact.

General disorders and administration site conditions

Uncommon (≥0.1% to <1%): medication residue.

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

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.

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

Serious adverse effects following inadvertent ingestion with the brimonidine 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. All subjects were reported to have made a full recovery, usually within 6-24 hours.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Ophthalmologicals, Antiglaucoma preparation and miotics ATC code: S01EC54

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.

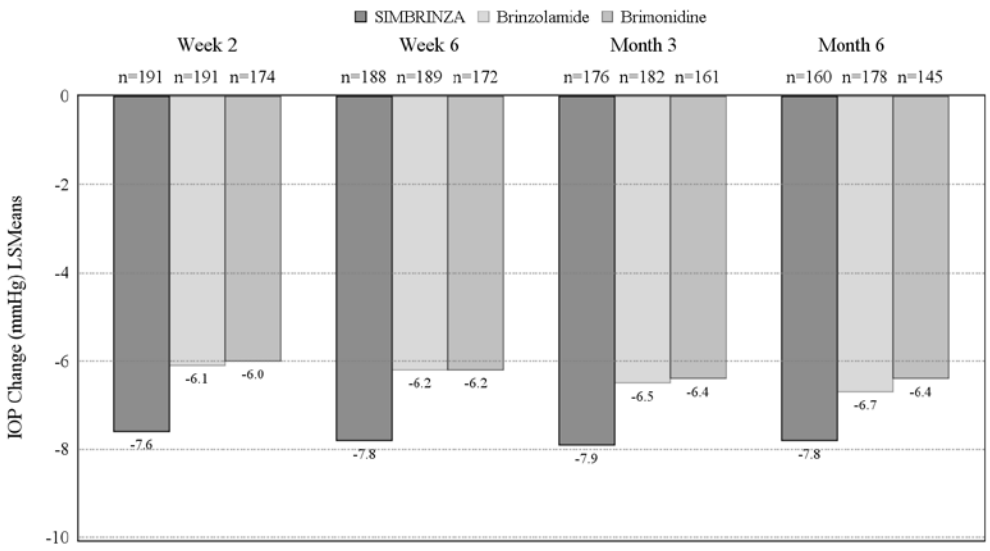
Pharmacodynamic effects

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.

Clinical efficacy and safety

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 10mg/mL + brimonidine 2mg/mL dosed concomitantly with respect to mean diurnal IOP reduction from baseline was demonstrated at all visits throughout the study (Table 1).

Table 1. 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 the Simbrinza group and 71.6% brinzolamide + brimonidine groups.

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.

5.2 Pharmacokinetic properties

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.

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.

Biotransformation

Brinzolamide is metabolized 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. Brinzolamide and N-desethylbrinzolamide do not inhibit cytochrome P450 isozymes at concentrations at least 100-fold above maximum systemic levels.

Brimonidine is extensively metabolized 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.

Elimination

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 30%), primarily as metabolites.

Brimonidine is primarily eliminated in the urine as metabolites. In rats and monkeys, urinary metabolites accounted for 60 to 75% of oral or intravenous doses.

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.

5.3 Preclinical safety data

Pregnancy

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. No treatment-related malformations were seen. Exposure levels are much lower following topical administration of brinzolamide. There are no adequate and well controlled studies using brinzolamide in pregnant women. The potential risk for humans is unknown.

Brimonidine

Animal studies with oral brimonidine do not indicate direct harmful effects with respect to reproductive toxicity. In animal studies, brimonidine crossed the placenta and entered into the foetal circulation to a limited extent. .

Breast-feeding

Studies in animals have shown that following oral administration, brinzolamide and brimonidine are 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 prenatal and postnatal study in which rats were given brinzolamide by oral gavage at doses up to 15 mg/kg/day.

Fertility

Studies in rats, in which animals were treated orally with brinzolamide up to 18 mg/kg/day, showed no adverse effects on male or female fertility. Nonclinical data do not show any effects of brinzolamide or brimonidine on fertility.

Carcinogenicity

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

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.

Mutagenicity

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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Benzalkonium chloride (as a preservative)

Propylene glycol

Carbomer 974P

Boric acid

Mannitol

Sodium chloride

Tyloxapol

Hydrochloric acid and/or sodium hydroxide to adjust pH

Purified water.

6.2 Incompatibilities

Unknown.

6.3 Shelf life

8 mL bottle: 24 months from the date of manufacture.

4 mL bottle: 12 months from the date of manufacture.

6.4 Special precautions for storage

Simbrinza should be stored below 25ºC. Discard 4 weeks after opening.

6.5 Nature and contents of container

4 mL round opaque low density polyethylene (LDPE) bottles with a LDPE dispensing plug and white polypropylene screw cap (Drop-Tainer®) containing 2.5 mL suspension.

8 mL round opaque low density polyethylene (LDPE) bottles with a LDPE dispensing plug and white polypropylene screw cap (Drop-Tainer®) containing 5 mL suspension.

6.6 Special precautions for disposal

Not applicable

7. MEDICINE SCHEDULE

Prescription Only Medicine

8. SPONSOR

Novartis New Zealand Limited

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Newmarket

Auckland 1149

New Zealand.

Free Phone: 0800 354 335

9. DATE OF FIRST APPROVAL

7 July 2016

10. DATE OF REVISION OF THE TEXT

30 September 2020

Summary Table of Changes

Section changed	**Summary of new information**
8. Sponsor	Removed Sponsor's old address

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