NOVARTIS

Simbrinza

(brinzolamide 10 mg/brimonidine tartrate 2 mg per mL)

Eye drops, suspension

Professional Information

Document status: Final

Release date: 06 February 2023

SCHEDULING STATUS **S3**

1 NAME OF THE MEDICINE

SIMBRINZA 10 mg/mL + 2 mg/mL eye drops, suspension

2 QUALITIVE AND QUANTITIVE COMPOSITION

Each mL contains 10 mg of brinzolamide and 2 mg of brimonidine tartrate.

Excipient with known effect:

Each mL contains 0,03 mg (0,003 %) of benzalkonium chloride as preservative.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Eye drops, suspension

White to-off-white uniform suspension, pH 6,5 (approximately)

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 Posology and method of administration

Posology

Use in adults, including the elderly

The recommended dose is one drop of SIMBRINZA in the affected eye(s) two times daily.

Missed dose

If a dose is missed, treatment should be continued with the next dose as planned.

Hepatic and/or renal impairment

SIMBRINZA has not been studied in patients with hepatic impairment and caution is therefore recommended in this population *(see section 4.4).*

SIMBRINZA has not been studied in patients with severe renal impairment (CrCl <30 mL/min) or in patients with hyperchloraemic acidosis. Since the brinzolamide component of SIMBRINZA and its metabolite are excreted predominantly by the kidney, SIMBRINZA is contraindicated in such patients *(see section 4.3).*

Paediatric population

The safety and efficacy of SIMBRINZA in children and adolescents aged 2 to 17 years have not been established. No data are available.

SIMBRINZA is contraindicated in neonates and infants aged less than 2 years.

Method of administration

For ocular use.

Patients should be instructed to shake the bottle gently before use.

When nasolacrimal occlusion is used and the eyelids are closed for 2 minutes, systemic absorption is reduced. This may result in a decrease in systemic side effects and an increase in local activity *(see section 4.4).*

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. Patients should be instructed to keep the bottle tightly closed when not in use.

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

4.3 Contraindications

- Hypersensitivity to the active substance(s) or to any of the excipients listed in section 6.1.
- Hypersensitivity to sulphonamides *(see section 4.4).*
- Patients receiving monoamine oxidase (MAO) inhibitor therapy *(see section 4.5).*
- Patients on antidepressants which affect noradrenergic transmission (e.g., tricyclic antidepressants and mianserin) *(see section 4.5).*
- Patients with severe renal impairment *(see section 4.4).*
- Patients with hyperchloraemic acidosis.
- Neonates and infants under the age of 2 years *(see section 4.4).*

4.4 Special warnings and precautions for use

The medicine should not be injected.

Patients should be instructed not to swallow SIMBRINZA.

Ocular effects

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

- The possible effect 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 *(for further instructions on wearing contact lenses, see below under "Benzalkonium chloride").* Careful monitoring of patients with compromised corneas, such as patients with diabetes mellitus or corneal dystrophies, is recommended.
- 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.
- The potential effects following cessation of treatment with SIMBRINZA have not been studied. While the duration of IOP-lowering effect for SIMBRINZA has not been studied, the IOP-lowering effect of brinzolamide is expected to last for 5-7 days. The IOP-lowering effect of brimonidine may be longer.

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. 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 medicine 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 medicine such as antihypertensives and/or cardiac glycosides concomitantly with SIMBRINZA or in patients with severe or unstable and uncontrolled cardiovascular disease *(see section 4.5).*

SIMBRINZA should be used with caution in patients with depression, cerebral or coronary insufficiency, Raynaud's phenomenon, orthostatic hypotension or thromboangiitis obliterans. Patients using IOP-lowering medication should be routinely monitored for IOP.

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 *(see section 4.5).*

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 *(see section 4.3).*

Hepatic impairment

SIMBRINZA has not been studied in patients with hepatic impairment; caution should be used in treating such patients *(see section 4.2)*.

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 this may therefore occur with topical administration *(see section 4.7).*

Paediatric population

The safety and efficacy of SIMBRINZA in children and adolescents aged 2 to 17 years have not been established. Symptoms of brimonidine overdose (including loss of consciousness/coma, hypotension, hypotonia, bradycardia, hypothermia, cyanosis, apnoea, lethargy, pallor, respiratory depression and somnolence) have been reported in neonates and infants receiving brimonidine eye drops as part of medical treatment of congenital glaucoma. SIMBRINZA is therefore contraindicated in children below 2 years of age *(see section 4.3).*

Treatment of children 2 years and above (especially those in the 2-7 age range and/or weighing <20 kg) is not recommended because of the potential for central nervous system-related side effects *(see section 4.9).*

Benzalkonium chloride

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

Benzalkonium chloride has been reported to cause eye irritation and symptoms of dry eyes and may affect the tear film and corneal surface. It should be used with caution in dry eye patients and in patients whose cornea may be compromised. Patients should be monitored in case of prolonged use.

As the possibility of adverse effects on the corneal permeability, and the danger of disruption of the corneal epithelium with prolonged or repeated usage of benzalkonium chloride preserved ophthalmological preparations cannot be excluded, regular ophthalmological examination is required. Caution should be exercised in the use of benzalkonium chloride preserved topical medication over an extended period in patients with extensive ocular surface disease.

4.5 Interaction with other medicines and other forms of interaction

- No specific medicine interaction studies have been performed with SIMBRINZA.
- SIMBRINZA is contraindicated in patients receiving monoamine oxidase inhibitors and in patients on antidepressants which affect noradrenergic transmission (e.g., tricyclic antidepressants and mianserin) *(see section 4.3).* Tricyclic antidepressants may blunt the ocular hypotensive response of SIMBRINZA.
- Caution is advised due to the possibility of an additive or potentiating effect with CNS depressants (e.g., alcohol, barbiturates, opiates, sedatives or anaesthetics).
- No data on the level of circulating catecholamines after SIMBRINZA administration are available. However, caution is advised in patients taking medicines which can affect the metabolism and uptake of circulating amines (e.g., chlorpromazine, methylphenidate, reserpine, serotonin-norepinephrine reuptake inhibitors).

- 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 medicines such as beta-blockers (ophthalmic and systemic), antihypertensives and/or cardiac glycosides e.g., digoxin concomitantly with SIMBRINZA.
- Caution is advised when initiating (or changing the dose of) concomitant systemic medicines (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).
- Brinzolamide 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 receiving an oral carbonic anhydrase inhibitor and topical brinzolamide. The concomitant administration of SIMBRINZA and oral carbonic anhydrase inhibitors is not recommended.
- 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

The safety of SIMBRINZA in pregnancy have not been established.

Use of SIMBRINZA is not recommended during pregnancy and in women of childbearing potential not using contraception.

Brinzolamide was not teratogenic in rats and rabbits, following systemic administration (oral gavage). 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 *(see section 5.3)*.

Breastfeeding

SIMBRINZA should not be used by women who are breastfeeding their infants.

Animal studies have shown that following oral administration, minimal levels of brinzolamide are excreted in breastmilk, and that brimonidine administered orally is excreted in breastmilk.

Fertility

Non-clinical data do not show any effects of brinzolamide or brimonidine on fertility. There are no data on the effect of topical ocular administration of SIMBRINZA on human fertility.

4.7 Effects on ability to drive and use machines

SIMBRINZA has a moderate influence on the ability to drive and use machines.

SIMBRINZA may cause dizziness, fatigue and/or drowsiness, which may impair the ability to drive or use machines.

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 machines.

Oral carbonic anhydrase inhibitors may impair the ability of elderly patients to perform tasks requiring mental alertness and/or physical coordination *(see section 4.4).*

4.8 Undesirable effects

a. Summary of the safety profile

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, and dysgeusia (bitter or unusual taste in the mouth following instillation) occurring in approximately 3 % of patients.

Tabulated summary of adverse reactions

The following adverse reactions have been reported during clinical studies with SIMBRINZA twice-daily dosing and during clinical studies and post-marketing surveillance with the individual components brinzolamide and brimonidine. They 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 <1/1000), very rare (<1/10 000) or not known (cannot be estimated from the available data). Within each frequency-grouping, adverse reactions are presented in order of decreasing seriousness.

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 cells 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], nightmares[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], hypoaesthesia 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]
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], rhinorrhoea[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 maculopapular[2], pruritus generalised[2], alopecia[2], skin tightness[2] Not known: face oedema[3], dermatitis[2,3], erythema[2,3] Stevens-Johnson syndrome (SJS), Toxic epidermal necrolysis (TEN)
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	

Description of selected adverse reactions

Dysgeusia was the most common systemic adverse reaction associated with the use of SIMBRINZA (3,4 %). It is likely to be caused by passage of the eye drops in the nasopharynx via the nasolacrimal canal and is mainly attributable to the brinzolamide component of SIMBRINZA. Nasolacrimal occlusion or gently closing the eyelid after instillation may help reduce the occurrence of this effect *(see section 4.2).*

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.

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 dosed with SIMBRINZA experienced decreases in blood pressure similar to those observed with the use of brimonidine as monotherapy.

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 providers are asked to report any suspected adverse reactions to SAHPRA via the **"6.04 Adverse Drug Reactions Reporting Form"**, found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

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

Due to the brinzolamide component of SIMBRINZA, electrolyte imbalance, development of an acidotic state, and possible nervous system effects may occur. Serum electrolyte levels (particularly potassium) and blood pH levels must be monitored.

There is very limited information regarding accidental ingestion with the brimonidine component of SIMBRINZA in adults. The only adverse reaction reported to date was hypotension. It was reported that the hypotensive episode was followed by rebound hypertension.

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 reactions 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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 15.4 Ophthalmic preparations, other

Mechanism of action

SIMBRINZA contains two active substances: brinzolamide and brimonidine tartrate. These two components lower intraocular pressure (IOP) in patients with open-angle glaucoma (OAG) and ocular hypertension (OHT) 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 (CA-II) 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, administration of brimonidine results in an increase in uveoscleral outflow.

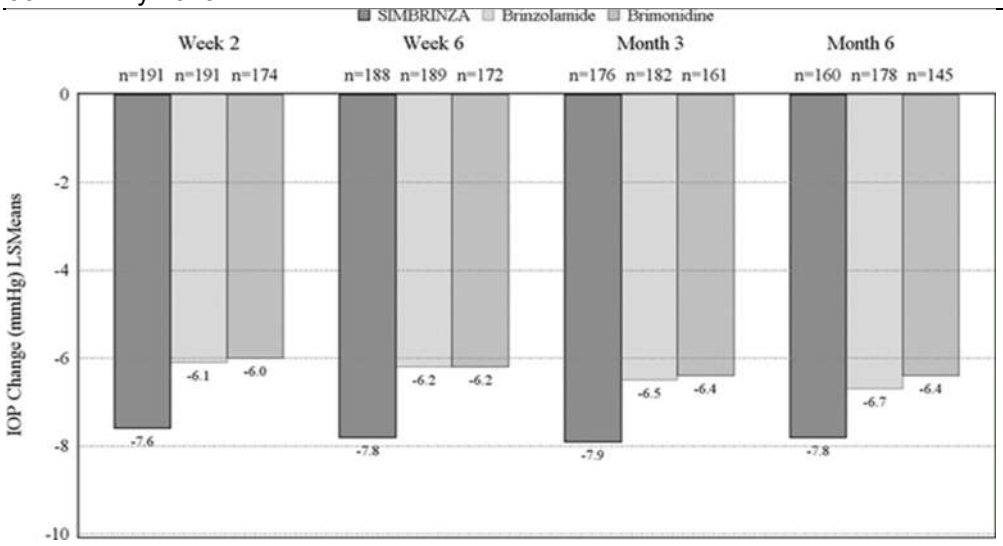
Pharmacodynamic effects

Clinical efficacy and safety

In a 6-month, controlled, contribution of elements clinical study 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 medicines, and who had mean baseline diurnal IOP of 26 mmHg, the mean diurnal IOP- lowering effect of brinzolamide/brimonidine tartrate dosed twice daily was approximately 8 mmHg.

Statistically superior reductions in the mean diurnal IOP were observed with brinzolamide/brimonidine tartrate compared to brinzolamide 10 mg/mL or brimonidine 2 mg/mL dosed twice daily 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 (brinzolamide/brimonidine tartrate 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 brinzolamide/brimonidine tartrate (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 brinzolamide/brimonidine tartrate ranged from 23 to 34 %. The percentages of patients with an IOP measurement less than 18 mmHg were greater in the Brinzolamide/Brimonidine tartrate group than in the Brinzolamide group at 9 of 12 assessments through Month 6 and were greater in the Brinzolamide/Brimonidine tartrate 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 61,7 % in the Brinzolamide/Brimonidine tartrate group, 40,1 % in the Brinzolamide group, and 40,0 % 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 medicines, and who had mean baseline diurnal IOP of 26 to 27 mmHg, non-inferiority of brinzolamide/brimonidine tartrate compared to brinzolamide 10 mg/mL + brimonidine 2 mg/mL dosed concomitantly was demonstrated at all visits throughout the study with respect to mean diurnal IOP reduction from baseline (Table 1).

Table 1 Comparison of mean diurnal IOP (mmHg) change from baseline – Non-inferiority study

Visit	Brinzolamide/ Brimonidine tartrate Mean[a]	Brinzolamide + Brimonidine Mean[a]	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 brinzolamide/brimonidine tartrate or the individual components administered concomitantly were similar (7 to 10 mmHg). Mean percent IOP reductions from baseline with brinzolamide/brimonidine tartrate 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 Brinzolamide/Brimonidine tartrate and Brinzolamide + Brimonidine groups. 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 65,6 % in the Brinzolamide/Brimonidine tartrate group and 63,7 % in the Brinzolamide + Brimonidine groups.

Paediatric population

See section 4.2 for information on paediatric use.

5.2 Pharmacokinetic properties

Absorption

Brinzolamide is absorbed through the cornea following topical ocular administration. The substance is also absorbed into the systemic circulation, where it binds strongly to carbonic anhydrase in red blood cells (RBCs). Plasma concentrations are very low. Whole blood elimination half-life is prolonged (>100 days) in humans due to RBC 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 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 brinzolamide/brimonidine tartrate administered two or three times daily to brinzolamide and brimonidine administered individually using the same two posologies, 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 were similar to those observed for

brimonidine administered alone, with the exception of the twice daily Brinzolamide/Brimonidine tartrate treatment group, for which the mean $AUC_{0\text{-}12\ hours}$ was about 25 % lower than that for brimonidine alone administered twice daily.

Distribution

Studies in rabbits showed that maximum brinzolamide ocular 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 (about 60 %) bound 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 it to be well-tolerated and safe during chronic administration.

Biotransformation

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

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.

Elimination

Brinzolamide is primarily eliminated in urine unchanged. 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.

Pharmacokinetic/pharmacodynamic relationship(s)

Brinzolamide/brimonidine tartrate is intended for local action within the eye. Assessment of human ocular exposure at efficacious doses is not feasible. The pharmacokinetic/pharmacodynamics 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 brinzolamide/brimonidine tartrate. 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 RBC concentrations of substance-related material did not inhibit RBC 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

Brinzolamide

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential.

Effects in non-clinical reproduction and development toxicity studies were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use. In rabbits oral, maternally toxic doses of brinzolamide of up to 6

mg/kg/day (261 times the recommended daily clinical dose of 23 µg/kg/day) revealed no effect on foetal development. In rats, doses of 18 mg/kg/day (783 times the recommended daily clinical dose), but not 6 mg/kg/day, resulted in slightly reduced ossification of skull and sternebrae of foetuses. These findings were associated with metabolic acidosis with decreased body weight gain in dams and decreased foetal weights. Dose related decreases in foetal weights were observed in pups of dams given 2 to 18 mg/kg/day. During lactation, the no adverse effect level in the offspring was 5 mg/kg/day.

Brimonidine

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Benzalkonium chloride

Propylene glycol

Carbomer 974P

Boric acid

Mannitol

Sodium chloride

Tyloxapol

Hydrochloric acid and/or sodium hydroxide (to adjust pH)

Purified water

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years

30 days after first opening.

6.4 Special precautions for storage

Do not store above 30 ºC.

6.5 Nature and contents of container

A white, low-density polyethylene (LDPE) bottle with a natural LDPE dispensing plug and white polypropylene (PP) closure containing 5 mL suspension.

6.6 Special precautions for disposal of a used medicine or waste materials derived from such medicine and other handling of the product

No special requirements for disposal.

7 THE HOLDER OF THE CERTIFICATE OF REGISTRATION

Novartis South Africa (Pty) Ltd.

Magwa Crescent West

Waterfall City

Jukskei View

Johannesburg, 2090

8 REGISTRATION NUMBER(S)

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

07 September 2021

10 DATE OF REVISION OF TEXT

06 February 2023

Botswana: S2	Namibia: NS2	Zimbabwe: P.P
Reg. No.: BOT1903607	Reg. No.: 16/15.4/0209	Reg. No.: 2017/19.1/5324