



**BRINZOLAMIDE**  
**Brimonidine Tartrate**

**SIMBRINZA\***  
10 mg / 2 mg per mL  
Sterile Ophthalmic Suspension (Drops)  
Anti-Glaucoma

## DESCRIPTION AND COMPOSITION

### Pharmaceutical form

Sterile Ophthalmic Suspension

### Active substance(s)

One mL of the sterile ophthalmic suspension contains 10 mg of brinzolamide, and 2 mg brimonidine tartrate corresponding to 1.3 mg of brimonidine tartrate.

### Excipients

Excipient with known effect: 1 mL of the sterile ophthalmic suspension contains 0.03 mg of benzalkonium chloride.

Other excipients: propylene glycol, carbomer 974P, boric acid, mannitol, sodium chloride, tyloxapol, hydrochloric acid and/or sodium hydroxide and purified water.

Pharmaceutical formulations may vary between countries.

## INDICATIONS

Brinzolamide/ Brimonidine tartrate (Simbrinza) Sterile Ophthalmic Suspension is indicated for the reduction of elevated intraocular pressure (IOP) in adult patients with open angle glaucoma or ocular hypertension.

## DOSAGE REGIMEN AND ADMINISTRATION

### Dosage regimen

### General target population

#### Adults

The recommended dose for adults is 1 drop in the affected eye(s) up to 2 times 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 Brinzolamide/ Brimonidine tartrate (Simbrinza) Sterile Ophthalmic Suspension, the other agent should be discontinued and Brinzolamide/ Brimonidine tartrate (Simbrinza) Sterile Ophthalmic Suspension should be started the following day.

Brinzolamide/ Brimonidine tartrate (Simbrinza) Sterile Ophthalmic Suspension may be used concomitantly with other topical ophthalmic medicinal products to lower intraocular pressure. If more than 1 topical ophthalmic medicinal product is being used, the medicines must be administered at least 5 minutes apart. Eye Ointments should be administered last.

### **Special populations**

#### **Pediatric patients (below 18 years)**

- Brinzolamide/ Brimonidine tartrate (Simbrinza) Sterile Ophthalmic Suspension is contraindicated in children less than 2 years of age.
- Brinzolamide/ Brimonidine tartrate (Simbrinza) Sterile Ophthalmic Suspension is not recommended in children or adolescents aged 2 to 17 years.

#### **Geriatric patients (65 years of age or above)**

- There are no special precautions to be followed in prescribing Brinzolamide/ Brimonidine tartrate (Simbrinza) Sterile Ophthalmic Suspension for the elderly.

#### **Method of administration**

- For ocular use.
- Patients should be instructed to shake the bottle well before use.
- After cap is removed, if tamper evident snap collar is loose, this should be removed before using the product. [Only applicable for Eye Drops containing a snap collar]
- To avoid contamination, the dropper tip should not touch any surface. The dropper tip should also not come into contact with the eye as this may cause injury to the eye. Patients should be instructed to keep the bottle tightly closed when not in use.
- Nasolacrimal occlusion and closing the eyelid for 2 minutes after instillation is recommended. This may result in a decrease in systemic side effects and an increase in local activity.
- Patients must be instructed to remove soft contact lenses prior to application of Brinzolamide/ Brimonidine tartrate (Simbrinza) Sterile Ophthalmic Suspension and to wait 15 minutes after instillation of the dose before reinsertion.

### **CONTRAINDICATIONS**

- Hypersensitivity to the active substances or to any of the excipients or to sulphonamides.
- Patients receiving monoamine oxidase (MAO) inhibitor therapy.
- Severe renal impairment.
- Hyperchloremic acidosis.
- Neonates and infants younger than 2 years old (see section WARNINGS AND PRECAUTIONS).

## **WARNINGS AND PRECAUTIONS**

- Like other topically applied ophthalmic agents, brinzolamide and brimonidine tartrate are absorbed systemically. Systemic absorption can be minimized by nasolacrimal occlusion (see section DOSAGE REGIMEN AND ADMINISTRATION).
- Brinzolamide/ Brimonidine tartrate (Simbrinza) Sterile Ophthalmic Suspension contains brimonidine tartrate which 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.
- Brinzolamide/ Brimonidine tartrate (Simbrinza) Sterile Ophthalmic Suspension contains brinzolamide, a sulphonamide. Hypersensitivity reactions common to all sulphonamide derivatives can occur in patients receiving Brinzolamide/ Brimonidine tartrate (Simbrinza) Sterile Ophthalmic Suspension as it is absorbed systemically. If signs of serious reactions or hypersensitivity occur, use of this product should be discontinued.
- The possible role of brinzolamide on corneal endothelial function has not been investigated in patients with compromised corneas (particularly in patients with low endothelial cell count). Carbonic anhydrase inhibitors may affect corneal hydration, which may lead to a corneal decompensation and oedema. Careful monitoring of patients with compromised corneas, such as patients with diabetes mellitus or corneal dystrophies, is recommended.
- Acid-base disturbances have been reported with oral carbonic anhydrase inhibitors. Brinzolamide/ Brimonidine tartrate (Simbrinza) Sterile Ophthalmic Suspension should be used with caution in patients with risk of renal impairment because of the possible risk of metabolic acidosis.
- Brinzolamide/ Brimonidine tartrate (Simbrinza) Sterile Ophthalmic Suspension has not been studied in patients with hepatic impairment; caution should be exercised in treating such patients.
- Brinzolamide/ Brimonidine tartrate (Simbrinza) Sterile Ophthalmic Suspension has a minimal effect on blood pressure of patients in clinical studies, caution should be taken in treating patients with severe cardiovascular disorders due to the brimonidine tartrate component.
- Brinzolamide/ Brimonidine tartrate (Simbrinza) Sterile Ophthalmic Suspension should be used with caution in patients with depression, cerebrovascular or coronary insufficiency, Raynaud's disease, orthostatic hypotension or thromboangiitis obliterans due to the brimonidine tartrate component.

### **Pediatric population**

Brinzolamide/ Brimonidine tartrate (Simbrinza) Sterile Ophthalmic Suspension is not recommended in children or adolescents aged 2 to 17 years because of the potential for CNS depression due to the brimonidine tartrate component (see section OVERDOSAGE). Brinzolamide/ Brimonidine tartrate (Simbrinza) Sterile Ophthalmic Suspension is contraindicated in children under 2 years of age (see section CONTRAINDICATIONS).

### **Contact lenses**

Benzalkonium chloride may cause eye irritation and is known to discolor soft contact lenses. Patients must be instructed to remove contact lenses prior to application of Brinzolamide/

Brimonidine tartrate (Simbrinza) Sterile Ophthalmic Suspension and to wait at least 15 minutes before reinsertion.

## ADVERSE DRUG REACTIONS

### Tabulated summary of adverse drug reactions from clinical trials

Adverse drug reactions from clinical trials (Table 1) are listed by MedDRA system organ class. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness. In addition, the corresponding frequency category for each adverse drug reaction is based on the following convention (CIOMS III): very common ( $\geq 1/10$ ); common ( $\geq 1/100$  to  $< 1/10$ ); uncommon ( $\geq 1/1,000$  to  $< 1/100$ ); rare ( $\geq 1/10,000$  to  $< 1/1,000$ ); very rare ( $< 1/10,000$ ).

**Table 1 Percentage of patients with adverse drug reactions in clinical trials**

System organ classification	Adverse drug reaction	Frequency category
Nervous system disorders	somnolence, dysgeusia	Common
	dizziness, headache	Uncommon
Eye disorders	conjunctivitis, conjunctivitis allergic, eye allergy, vision blurred, eye pain, eye irritation, dry eye, eye pruritus, ocular hyperaemia blepharitis, ocular discomfort	Common
	corneal erosion, keratitis, punctate keratitis, blepharitis allergic, conjunctival follicle, photophobia, eye discharge, lacrimation increased, asthenopia, erythema of eyelid	Uncommon
	visual acuity reduced, lacrimation decreased	Rare
Ear and labyrinth disorders	vertigo	Uncommon
Vascular disorders	hypotension, blood pressure decreased	Uncommon
Respiratory, thoracic and mediastinal disorders	nasal dryness	Uncommon
	upper-airway cough syndrome, nasal congestion, dry throat	Rare
Gastrointestinal disorders	dry mouth	Common
	nausea, dyspepsia, abdominal discomfort	Rare
Skin and subcutaneous tissue disorders	dermatitis allergic	Uncommon
General disorders and administration site conditions	asthenia, fatigue, medication residue present	Uncommon

## INTERACTIONS

The following interactions are expected with Brinzolamide/ Brimonidine tartrate (Simbrinza) Sterile Ophthalmic Suspension due to potential drug interactions with the mono-components: Brinzolamide/ Brimonidine tartrate (Simbrinza) Sterile Ophthalmic Suspension is contraindicated in patients receiving monoamine oxidase inhibitors (see section CONTRAINDICATIONS).

- 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 (e.g. nonsteroidal anti-inflammatory

drugs (NSAIDs) and salicylates) must be considered in patients receiving Brinzolamide/ Brimonidine tartrate (Simbrinza) Sterile Ophthalmic Suspension.

- 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 Brinzolamide/ Brimonidine tartrate (Simbrinza) Sterile Ophthalmic Suspension and oral carbonic anhydrase inhibitors is not recommended.
- Alpha agonists, as a class, may reduce pulse and blood pressure. Caution is advised with concomitant use of drugs such as antihypertensive and/or cardiac glycosides with similar cardiovascular effects (drugs that cause hypotension).
- Caution is advised in patients taking tricyclic antidepressants as these agents may blunt the hypotensive response. No data on the level of circulating catecholamines after Brinzolamide/ Brimonidine tartrate (Simbrinza) Sterile Ophthalmic Suspension administration are available. Caution, however, is advised in patients taking medicinal products 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.
- Caution is advised when initiating (or changing the dose of) a concomitant systemic agent (irrespective of pharmaceutical form) which may interact with  $\alpha$ -adrenergic agonists or interfere with their activity i.e. agonists or antagonists of the adrenergic receptor (e.g. isoprenaline, prazosin).

## **PREGNANCY, LACTATION, FEMALES AND MALES OF REPRODUCTIVE POTENTIAL**

### **PREGNANCY**

#### **Risk summary**

There are no adequate and well controlled studies in pregnant women regarding the ocular use of Brinzolamide/ Brimonidine tartrate (Simbrinza) Sterile Ophthalmic Suspension.

Brinzolamide and brimonidine were not teratogenic in rats and rabbits following systemic administration.

In reproductive toxicity studies, brinzolamide administered orally to rats during organogenesis induced fetal toxicity at 375 times the maximum recommended ophthalmic human dose (MROHD) based on body weight (BW). In rabbits, no fetal toxicity was observed following oral brinzolamide administration during organogenesis at 125 times the MROHD based on BW (see Animal data).

Oral administration of brimonidine to rats and rabbits during organogenesis showed no evidence of teratogenicity and embryo toxicity at 107- and 27- times, respectively, the MRHOD based on plasma concentrations (see Animal data).

Brinzolamide/ Brimonidine tartrate (Simbrinza) Sterile Ophthalmic Suspension, should be used during pregnancy only if the potential benefit to the mother outweighs the potential risk to the fetus.

#### **Animal data**

## **Brinzolamide**

Embryofetal development studies were conducted in pregnant rats administered 0, 2, 6 or 18 mg/kg/day of brinzolamide by oral gavage on gestation days 6 to 17 to target the period of organogenesis. Decreased maternal weight gain was observed at 6 and 18 mg/kg/day. Decreased fetal body weight and reduced skeletal ossification were observed at 18 mg/kg/day (375 times the MROHD based on BW and 60 times the MROHD based on Body Surface Area (BSA)). The No-Observed effect level (NOEL) was 2 mg/kg/day (42 times the MROHD based on BW and 7 times the MROHD based on BSA).

Embryofetal development studies were conducted in pregnant rabbits administered 0, 1, 3, or 6 mg/kg/day of brinzolamide by oral gavage on gestation days 6 to 18 to target the period of organogenesis. Maternal weight loss during pregnancy was observed at  $\geq 3$  mg/kg/day (63 times the MROHD based on BW and 20 times the MROHD based on BSA). At 6 mg/kg/day, mortality, emaciation, lack of feces and abortions were noted in does. The NOEL for maternal toxicity was 1 mg/kg/day (21 times the MROHD based on BW and 7 times the MROHD based on BSA). No treatment-related fetal effects were observed up to the maximum tested dose of 6 mg/kg/day (125 times the MROHD based on BW and 41 times the MROHD based on BSA).

In a rat peri and postnatal development study, brinzolamide was orally administered at doses of 1, 5 and 15 mg/kg/day from gestation day 16 through lactation day 20. Decreases in food consumption and mean body weight gain was seen in the dams during gestation and lactation at 15 mg/kg/day. Decreased pup body weight was observed at 15 mg/kg/day (313 times the MROHD based on BW and 51 times the MROHD based on BSA). No indications of impaired behavior, fertility or reproductive capabilities were observed in the F1 generation. F2 growth and development appeared normal throughout lactation. The NOEL for maternal and developmental toxicity was 5 mg/kg/day (104 times the MROHD based on BW and 17 times the MROHD based on BSA).

Following oral administration of 1 mg/kg <sup>14</sup>C-brinzolamide to pregnant rats, radioactivity was found to cross the placenta and the levels of radioactivity in fetal tissues were 3- to 10 fold less than those measured in the dams.

## **Brimonidine**

In embryofetal development studies, pregnant rats were orally administered brimonidine at doses of 0.066, 0.66 or 1.650 mg base/kg/day on gestation days 6 to 15 to target the period of organogenesis. No evidence of teratogenicity or embryo lethality were observed. Reduction in body weight of dams at 0.66 and 1.65 mg base/kg/day and of pups (F1) at 1.65 mg base/kg/day were observed. Oral doses of 0.66 mg base/kg/day revealed no evidence of harm to the fetus corresponding to 107-times the maximal plasma concentrations (C<sub>max</sub>) in humans treated with one drop of Brinzolamide/ Brimonidine tartrate (Simbrinza) Sterile Ophthalmic Suspension in both eyes three times daily.

In embryofetal development studies, pregnant rabbits were orally administered brimonidine at doses of 0.165, 0.660 and 3.330 mg base/kg/day on gestation days 6 to 18 to targeting the period of organogenesis. No evidence of treatment-related embryotoxicity, fetal toxicity, or teratogenicity were observed up to the highest tested dose of 3.3 mg base/kg/day, corresponding to 27-times the C<sub>max</sub> in humans treated with one drop of Brinzolamide/ Brimonidine tartrate (Simbrinza) Sterile Ophthalmic Suspension in both eyes three times daily.

In a peri- and postnatal development study, brimonidine was administered orally to pregnant rats from gestation day 16 through lactation day 20. Reproductive capabilities (survival, development, and behavior) of F1 and F2 generations were not affected. The dose of brimonidine (0.66 mg/kg/day) was estimated to achieve area under the curve (AUC) values that correspond to 60-fold the estimated AUC in humans treated with one drop of brimonidine in both eyes three times daily.

After a single oral dose of 0.25 mg/kg <sup>14</sup>C-brimonidine in pregnant rats, radioactivity was found to cross the placenta and entered into the fetal circulation to a limited extent, producing <sup>14</sup>C-brimonidine concentrations in fetal blood that were 10-27% of that in maternal blood.

## **LACTATION**

### **Risk summary**

There are no data regarding the effects of brinzolamide or brimonidine tartrate on milk production of breast-feeding women or on the breastfed infant.

It is not known whether brinzolamide or brimonidine is transferred into human milk following topical ocular administration of Brinzolamide/ Brimonidine tartrate (Simbrinza) Sterile Ophthalmic Suspension. Brinzolamide and brimonidine have been detected in the milk of lactating rats following oral administration of brinzolamide and brimonidine respectively in two different studies (see Data).

A risk to the breastfed child cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from therapy, taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

### **Data**

#### **Animal data**

##### **Brinzolamide**

Following oral administration of 1 mg/kg <sup>14</sup>C-brinzolamide (21 times the MROHD) to lactating rats, radioactivity was found in milk at concentrations below those found in the rat blood and plasma.

##### **Brimonidine**

Following oral administration of 0.25 mg/kg <sup>14</sup>C-brimonidine (26 times the MROHD) to lactating rats, radioactivity was detected in milk at concentrations similar or higher than in the rat maternal plasma.

## **FEMALES AND MALES OF REPRODUCTIVE POTENTIAL**

### **Infertility**

Studies have not been performed to evaluate the effect of topical ocular administration of Brinzolamide/ Brimonidine tartrate (Simbrinza) Sterile Ophthalmic Suspension on human fertility. In rats, no effects on fertility were noted with brinzolamide (up to 375 times the MROHD based on BW) and brimonidine (up to 60-times the human AUC) (see section NON-CLINICAL SAFETY DATA). No effects on male or female fertility are anticipated from the

topical ocular use of Brinzolamide/ Brimonidine tartrate (Simbrinza) Sterile Ophthalmic Suspension.

## **OVERDOSAGE**

In case of accidental ingestion, effects of brinzolamide toxicity may include electrolyte imbalance, development of an acidotic state, and possible nervous system effects. Serum electrolyte levels (particularly potassium) and blood pH levels must be monitored.

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

Treatment of an overdose includes supportive and symptomatic therapy. The patient's airway should be maintained.

### **Pediatric population**

Serious adverse effects following inadvertent ingestion with the brimonidine tartrate component of Brinzolamide/ Brimonidine tartrate (Simbrinza) Sterile Ophthalmic Suspension by pediatric 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 apnea, and required admission to intensive care with intubation if indicated. All subjects were reported to have made a full recovery, usually within 6 to 24 hours.

## **CLINICAL PHARMACOLOGY**

### **Pharmacotherapeutic group, ATC**

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

### **Mechanism of action (MOA)**

Brinzolamide/ Brimonidine tartrate (Simbrinza) Sterile Ophthalmic Suspension is comprised of 2 components: brinzolamide (carbonic anhydrase inhibitor) and brimonidine tartrate (alpha-2 adrenergic receptor agonist). Each of these 2 components decreases elevated IOP by different mechanisms of action.

Brinzolamide is a topical ocular carbonic anhydrase inhibitor (CAI). Carbonic anhydrase is an enzyme found in many tissues of the body including the eye. CAIs inhibit carbonic anhydrase, mainly isozyme II, in the ciliary epithelium and reduce the production of bicarbonate ion, which is a critical component for active ion transport in aqueous formation. A reduction in bicarbonate ion by CAIs diminishes sodium and fluid transport across the ciliary epithelium, and decreases aqueous humor production. Brinzolamide has a peak ocular hypotensive effect occurring at 2 to 3 hours post dose.

Brimonidine, a selective alpha-2 adrenergic agonist, selectively activates the alpha-2 adrenergic receptor of the ciliary epithelium. Activation of this receptor activates the inhibitory GTP-binding protein, which then inhibits the enzyme adenylyl cyclase. This leads to a reduction in intracellular cyclic AMP levels and eventually suppresses aqueous humor production. It has been demonstrated that brimonidine also stimulates uveoscleral outflow. Initial administration of brimonidine reduces aqueous humor production. However, increase in uveoscleral outflow becomes the predominant effect with chronic administration.

Brimonidine tartrate has a peak ocular hypotensive effect occurring at 2 hours post dose.

The combination of brinzolamide/ brimonidine results in a reduction in IOP, a major risk factor in the pathogenesis of optic nerve damage and glaucomatous visual field loss.

## **Pharmacokinetics (PK)**

### **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 (RBCs). Plasma drug concentrations are low. Whole blood elimination half-life is prolonged (>100 days) in humans due to RBC carbonic anhydrase binding, resulting in significant accumulation of brinzolamide in the blood.

Plasma brimonidine concentrations achieve peak levels within 0.5 to 2.5 hours and decline with a systemic half-life of approximately 2 hours.

In a topical ocular clinical study comparing the systemic pharmacokinetics of brinzolamide/brimonidine Eye Drops, suspension 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 during a course of topical ocular twice daily administration, brinzolamide significantly accumulates in the iris-ciliary body (ICB), choroid, and especially retina, while brimonidine significantly accumulates in choroid, retina and especially the ICB. Data in pigmented rabbits topically administered radiolabeled brinzolamide showed highest ocular radioactivity levels in the ICB with maximum aqueous humor and choroid levels about 6-fold lower than those in the ICB. Peak retinal exposure was about 11-fold lower than that of the ICB.

Circulating brinzolamide is primarily bound to RBCs while the much lower concentrations in human plasma are about 60% protein-bound.

Accumulation of brimonidine in the iris, ciliary body, and choroid/retina was reported in cynomolgus monkeys when 0.5% brimonidine was administered twice daily topically in the eye. A similar trend was seen in pigmented rabbits, where extensive accumulation and prolonged retention were observed in iris-ciliary body and choroid. These phenomena are presumably due to the known melanin-binding properties of brimonidine.

### **Biotransformation/metabolism**

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 analog 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.

In humans, brimonidine is primarily metabolized by the liver, most likely by cytochrome P450 and aldehyde oxidase. The principle metabolic pathways of brimonidine are alpha(N)-oxidation to 2-oxobrimonidine, 3-oxobrimonidine and 2,3-dioxobrimonidine and oxidative cleavage of the imadazoline ring to yield 5-bromo-6-guanidinoquinoxaline.

### **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 20%), primarily as metabolites.

In humans, brimonidine tartrate is eliminated rapidly via extensive systemic metabolism; there is no marked systemic accumulation after multiple dosing. Urinary excretion is the major route of elimination of the drug and its metabolites. Approximately 87% of an orally-administered radioactive dose was eliminated within 120 hours, with 74% found in the urine in the first 96 hours.

### **Linearity/non-linearity**

Due to its tight and saturable binding to carbonic anhydrase in RBCs and various tissues, the pharmacokinetics of brinzolamide are inherently non-linear. In contrast, brimonidine kinetics are linear as evidenced by aqueous humor data from cataract patients showing a dose-proportional increase in ocular exposure with increasing topical dose.

### **Pharmacokinetic/pharmacodynamic relationship(s)**

Although brinzolamide has prolonged retention in the ICB and other tissues containing carbonic anhydrase with half-lives >30 days in the ICB of both pigmented and albino rabbits, its IOP-lowering effect is considerably shorter (about 12 hours). This is due to the fact that >99% of carbonic anhydrase must be bound to drug for the pharmacological effects to be observed.

Increased IOP-lowering efficacy with increasing brimonidine dose was demonstrated following administration after single topical administrations of 0.08, 0.2 or 0.5% brimonidine solution to patients with glaucoma or ocular hypertension, with mean IOP reductions from baseline ranging from 16.1 to 30.1% across the dose range.

## **CLINICAL STUDIES**

### **Data from twice daily studies**

#### ***Monotherapy***

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 medicinal products, and who had mean baseline diurnal IOP of 26 mmHg, the mean diurnal IOP-lowering effect of Brinzolamide/ Brimonidine tartrate (Simbrinza) Sterile Ophthalmic Suspension dosed twice daily was approximately 8 mmHg. Statistically superior reductions in the mean diurnal IOP were observed with Brinzolamide/ Brimonidine tartrate (Simbrinza) Sterile Ophthalmic Suspension

compared to brinzolamide 10 mg/mL or brimonidine 2 mg/mL dosed twice daily at all visits throughout the study. Mean IOP reductions from baseline at each time point at each visit were greater with Brinzolamide/ Brimonidine tartrate (Simbrinza) Sterile Ophthalmic Suspension (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 (Simbrinza) Sterile Ophthalmic Suspension ranged from 23 to 34%. The percentages of patients with an IOP measurement less than 18 mmHg were greater in the Brinzolamide/ Brimonidine tartrate (Simbrinza) Sterile Ophthalmic Suspension group than in the brinzolamide group at 11 of 12 assessments through Month 6 and were greater in the Brinzolamide/ Brimonidine tartrate (Simbrinza) Sterile Ophthalmic Suspension 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 Brinzolamide/ Brimonidine tartrate (Simbrinza) Sterile Ophthalmic Suspension 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 medicinal products, and who had mean baseline diurnal IOP of 26 to 27 mmHg, non-inferiority of Brinzolamide/ Brimonidine tartrate (Simbrinza) Sterile Ophthalmic Suspension 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. Mean IOP reductions from baseline at each time point at each visit with Brinzolamide/ Brimonidine tartrate (Simbrinza) Sterile Ophthalmic Suspension or the individual components administered concomitantly were similar (7 to 10 mmHg). Mean percent IOP reductions from baseline with Brinzolamide/ Brimonidine tartrate (Simbrinza) Sterile Ophthalmic Suspension 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 (Simbrinza) Sterile Ophthalmic Suspension 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 71.6% in both study groups.

### ***Adjunct therapy***

Clinical data on the use of Brinzolamide/ Brimonidine tartrate (Simbrinza) Sterile Ophthalmic Suspension adjunctive to prostaglandin analogs (PGA) also showed superior IOP-lowering efficacy of Brinzolamide/ Brimonidine tartrate (Simbrinza) Sterile Ophthalmic Suspension + PGA compared with the PGA alone. In study CQVJ499A2401, Brinzolamide/ Brimonidine tartrate (Simbrinza) Sterile Ophthalmic Suspension + PGA (i.e., travoprost, latanoprost, or bimatoprost) demonstrated superior IOP-lowering efficacy from baseline compared to Vehicle + PGA after 6 weeks of treatment, with between-treatment difference in model adjusted mean change from baseline in diurnal IOP of -3.44 mmHg (95% CI, -4.2, -2.7; p-value <0.001).

Clinical data on the use of Brinzolamide/ Brimonidine tartrate (Simbrinza) Sterile Ophthalmic Suspension adjunctive to travoprost-timolol maleate fixed dose combination eye drops, solution also showed superior IOP-lowering efficacy of Brinzolamide/ Brimonidine tartrate (Simbrinza) Sterile Ophthalmic Suspension+ travoprost-timolol maleate eye drops compared with the travoprost-timolol maleate alone. In study CQVJ499A2402, Brinzolamide/ Brimonidine

tartrate (Simbrinza) Sterile Ophthalmic Suspension + travoprost-timolol maleate eye drops demonstrated superior IOP-lowering efficacy from baseline compared to Vehicle + travoprost-timolol maleate eye drops after 6 weeks of treatment, with between-treatment difference in model adjusted mean change from baseline in diurnal IOP of -2.15 mmHg (95% CI, -2.8, -1.5; p-value <0.001).

The safety profile of Brinzolamide/ Brimonidine tartrate (Simbrinza) Sterile Ophthalmic Suspension in adjunct therapy was similar to that observed with Brinzolamide/ Brimonidine tartrate (Simbrinza) Sterile Ophthalmic Suspension monotherapy.

#### **Data from three times daily studies**

##### ***Monotherapy***

Two clinical trials of 3 months duration were conducted in patients with open-angle glaucoma or ocular hypertension to compare the IOP-lowering effect of Brinzolamide/ Brimonidine tartrate (Simbrinza) Sterile Ophthalmic Suspension dosed three times daily to individually administered 1% brinzolamide three times daily and 0.2% brimonidine tartrate three times daily (TID).

The IOP-lowering effect of Brinzolamide/ Brimonidine tartrate (Simbrinza) Sterile Ophthalmic Suspension was 1 to 3 mmHg greater than monotherapy with either 1% brinzolamide or 0.2% brimonidine tartrate throughout the duration of the trials.

##### ***Adjunct therapy***

Clinical data on the use of Brinzolamide/ Brimonidine tartrate (Simbrinza) Sterile Ophthalmic Suspension adjunctive to PGA also showed superior IOP-lowering efficacy of Brinzolamide/ Brimonidine tartrate (Simbrinza) Sterile Ophthalmic Suspension + PGA compared with the PGA alone. In study M-13-019, Brinzolamide/ Brimonidine tartrate (Simbrinza) Sterile Ophthalmic Suspension + travoprost ophthalmic solution, 0.004% (adjunctive therapy to PGA) was superior to Vehicle + travoprost ophthalmic solution, 0.004% (PGA monotherapy) in lowering diurnal IOP at Week 6. The mean diurnal IOP was significantly less ( $p < 0.0001$ ) in patients treated with Brinzolamide/ Brimonidine tartrate (Simbrinza) Sterile Ophthalmic Suspension + travoprost ophthalmic solution, 0.004% than in patients treated with Vehicle + travoprost ophthalmic solution, 0.004% (LS mean diurnal IOP of 17.55 and 20.71 mmHg, respectively). The treatment group difference based upon LS means was -3.16 mmHg (CI = -4.16 to -2.27) in favor of Brinzolamide/ Brimonidine tartrate (Simbrinza) Sterile Ophthalmic Suspension + travoprost. In study M-13-020, Brinzolamide/ Brimonidine tartrate (Simbrinza) Sterile Ophthalmic Suspension + PGA (adjunctive therapy) was also superior to Vehicle + PGA (PGA monotherapy) in regard to mean diurnal IOP at Week 6. The mean diurnal IOP was significantly less ( $p < 0.0001$ ) in patients treated with Brinzolamide/ Brimonidine tartrate (Simbrinza) Sterile Ophthalmic Suspension + PGA than in patients treated with Vehicle + PGA (LS mean diurnal IOP of 17.07 and 20.51 mmHg, respectively). The treatment group difference based upon LS means was -3.44 mmHg (CI = -4.45 to -2.42) in favor of Brinzolamide/ Brimonidine tartrate (Simbrinza) Sterile Ophthalmic Suspension + PGA.

The safety profile of Brinzolamide/ Brimonidine tartrate (Simbrinza) Sterile Ophthalmic Suspension in adjunct therapy was similar to that observed with Brinzolamide/ Brimonidine tartrate (Simbrinza) Sterile Ophthalmic Suspension monotherapy.

## **NON-CLINICAL SAFETY DATA**

Non-clinical data for brinzolamide or brimonidine revealed no special hazard for humans based on single-dose toxicity, repeated-dose toxicity, genotoxicity, and carcinogenicity studies and topical ocular irritation studies. For information on reproductive and developmental toxicity, see section 9 Pregnancy, lactation, females and males of reproductive potential.

### **Brinzolamide**

In a rat fertility study, oral administration of brinzolamide did not reveal any adverse effects on the fertility or reproductive capacity of males or females at doses up to 18 mg/kg/day (up to 375 times the MROHD based on BW and 60 times the MROHD based on BSA).

### **Brimonidine**

In reproductive studies performed in rats with oral doses of 0.66 mg brimonidine base/kg/day (corresponding to 60-times the human AUC, following administration of one drop of 0.15% brimonidine to both eyes three times daily), fertility was not impaired.

## **INCOMPATIBILITIES**

Not applicable.

## **STORAGE**

Store at temperatures not exceeding 30°C.

Shake well before use.

Store the opened container at 25°C for 30 days.

Brinzolamide/ Brimonidine tartrate (Simbrinza) Sterile Ophthalmic Suspension should not be used after the date marked “EXP” on the pack.

Brinzolamide/ Brimonidine tartrate (Simbrinza) Sterile Ophthalmic Suspension must be kept out of the reach and sight of children.

## **INSTRUCTIONS FOR USE AND HANDLING**

There are no special requirements for use or handling of this product.

Information might differ in some countries.

## **AVAILABILITY**

5 mL LDPE bottle with a dispensing plug and polypropylene (PP) screwcap. (DROPTAINER\* dispensing bottle).

## **CAUTION:**

Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.

For suspected adverse drug reaction, report to the FDA: [www.fda.gov.ph](http://www.fda.gov.ph)

The patient is advised to seek IMMEDIATE medical attention at the first sign of adverse drug reaction.

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