HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use SIMBRINZA™ safely and effectively. See full prescribing information for SIMBRINZA™

SIMBRINZA™ (brinzolamide/brimonidine tartrate ophthalmic suspension) 1%/0.2%
Initial U.S. Approval: 2013

----------INDICATIONS AND USAGE----------
SIMBRINZA™ is a fixed combination of a carbonic anhydrase inhibitor and an alpha 2 adrenergic receptor agonist indicated for the reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension. (1)

----------DOSAGE AND ADMINISTRATION----------
Shake well before use. Instill one drop in the affected eye(s) three times daily. If more than one topical ophthalmic drug is being used, the drugs should be administered at least five (5) minutes apart. (2)

----------DOSAGE FORMS AND STRENGTHS----------
Suspension containing 10 mg/mL brinzolamide and 2 mg/mL brimonidine tartrate. (3)

----------CONTRAINDICATIONS----------
- Hypersensitivity to any component of this product. (4.1)
- Neonates and infants (under the age of 2 years). (4.2)

----------WARNINGS AND PRECAUTIONS----------
- Potential for sulfonamide hypersensitivity reactions because of the brinzolamide tartrate component (5.1)
- Potential for corneal endothelium cell loss (5.2)
- Severe renal impairment may limit the metabolism of the brinzolamide tartrate component (5.3)

----------ADVERSE REACTIONS----------
Most common adverse reactions occurring in approximately 3 to 5% of patients included blurred vision, eye irritation, dysgeusia (bad taste), dry mouth, eye allergy. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Alcon Laboratories, Inc. at 1-800-757-9195 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
- Oral Carbonic Anhydrase Inhibitors (7.1)
- High-dose Salicylate Therapy (7.2)
- CNS Depressants (7.3)
- Antihypertensives/Cardiac Glycosides (7.4)
- Tricyclic Antidepressants (7.5)
- Monoamine Oxidase Inhibitors (7.6)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 04/2013

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

SIMBRINZA™ (brinzolamide/brimonidine tartrate ophthalmic suspension) 1%/0.2% is a fixed combination of a carbonic anhydrase inhibitor and an alpha 2 adrenergic receptor agonist indicated for the reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension.

2 DOSAGE AND ADMINISTRATION

The recommended dose is one drop of SIMBRINZA™ in the affected eye(s) three times daily. Shake well before use. SIMBRINZA™ ophthalmic suspension may be used concomitantly with other topical ophthalmic drug products to lower intraocular pressure. If more than one topical ophthalmic drug is being used, the drugs should be administered at least five (5) minutes apart.

3 DOSAGE FORMS AND STRENGTHS

Suspension containing 10 mg/mL brinzolamide and 2 mg/mL brimonidine tartrate.

4 CONTRAINDICATIONS

4.1 Hypersensitivity

SIMBRINZA™ is contraindicated in patients who are hypersensitive to any component of this product.

4.2 Neonates and Infants (under the age of 2 years)

SIMBRINZA™ is contraindicated in neonates and infants (under the age of 2 years*) [see Use in Specific Populations (8.4)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Sulfonamide Hypersensitivity Reactions

SIMBRINZA™ contains brinzolamide, a sulfonamide, and although administered topically is absorbed systemically. Therefore, the same types of adverse reactions that are attributable to sulfonamides may occur with topical administration of SIMBRINZA™. Fatalities have occurred due to severe reactions to sulfonamides including Stevens-Johnson syndrome, toxic epidermal necrolysis, fulminant hepatic necrosis, agranulocytosis, aplastic anemia, and other blood dyscrasias. Sensitization may recur when a sulfonamide is re-administered irrespective of the route of administration. If signs of serious reactions or hypersensitivity occur, discontinue the use of this preparation *[see Patient Counseling Information (17.1)]*.

5.2 Corneal Endothelium

Carbonic anhydrase activity has been observed in both the cytoplasm and around the plasma membranes of the corneal endothelium. There is an increased potential for developing corneal edema in patients with low endothelial cell counts. Caution should be used when prescribing SIMBRINZA™ to this group of patients.

5.3 Severe Renal Impairment
SIMBRINZA™ has not been specifically studied in patients with severe renal impairment (CrCl < 30 mL/min). Since brinzolamide and its metabolite are excreted predominantly by the kidney, SIMBRINZA™ is not recommended in such patients.

5.4 Acute Angle-Closure Glaucoma
The management of patients with acute angle-closure glaucoma requires therapeutic interventions in addition to ocular hypotensive agents. SIMBRINZA™ has not been studied in patients with acute angle-closure glaucoma.

5.5 Contact Lens Wear
The preservative in SIMBRINZA™, benzalkonium chloride, may be absorbed by soft contact lenses. Contact lenses should be removed during instillation of SIMBRINZA™ but may be reinserted 15 minutes after instillation *[see Patient Counseling Information (17.7)]*.

5.6 Severe Cardiovascular Disease
Brimonidine tartrate, a component of SIMBRINZA™, has a less than 5% mean decrease in blood pressure 2 hours after dosing in clinical studies; caution should be exercised in treating patients with severe cardiovascular disease.

5.7 Severe Hepatic Impairment
Because brimonidine tartrate, a component of SIMBRINZA™, has not been studied in patients with hepatic impairment, caution should be exercised in such patients.

5.8 Potentiation of Vascular Insufficiency
Brimonidine tartrate, a component of SIMBRINZA™, may potentiate syndromes associated with vascular insufficiency. SIMBRINZA™ should be used with caution in patients with depression, cerebral or coronary insufficiency, Raynaud's phenomenon, orthostatic hypotension, or thromboangitis obliterans.

5.9 Contamination of Topical Ophthalmic Products After Use
There have been reports of bacterial keratitis associated with the use of multiple-dose containers of topical ophthalmic products. These containers have been inadvertently contaminated by patients who, in most cases, had a concurrent corneal disease or a disruption of the ocular epithelial surface *[see Patient Counseling Information (17.4)]*.

6 ADVERSE REACTIONS
6.1 Clinical Studies Experience
Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to the rates in the clinical studies of another drug and may not reflect the rates observed in practice.

SIMBRINZA™ In two clinical trials of 3 months duration 435 patients were treated with SIMBRINZA™, and 915 were treated with the two individual components. The most frequently reported adverse reactions in patients treated with SIMBRINZA™ occurring in approximately 3 to 5% of patients in descending order of incidence were blurred vision, eye irritation, dysgeusia

(bad taste), dry mouth, and eye allergy. Rates of adverse reactions reported with the individual components were comparable. Treatment discontinuation, mainly due to adverse reactions, was reported in 11% of SIMBRINZA™ patients.

Other adverse reactions that have been reported with the individual components during clinical trials are listed below.

Brinzolamide 1%

In clinical studies of brinzolamide ophthalmic suspension 1%, the most frequently reported adverse reactions reported in 5 to 10% of patients were blurred vision and bitter, sour or unusual taste. Adverse reactions occurring in 1 to 5% of patients were blepharitis, dermatitis, dry eye, foreign body sensation, headache, hyperemia, ocular discharge, ocular discomfort, ocular keratitis, ocular pain, ocular pruritus and rhinitis.

The following adverse reactions were reported at an incidence below 1%: allergic reactions, alopecia, chest pain, conjunctivitis, diarrhea, diplopia, dizziness, dry mouth, dyspnea, dyspepsia, eye fatigue, hypertonia, keratoconjunctivitis, keratopathy, kidney pain, lid margin crusting or sticky sensation, nausea, pharyngitis, tearing and urticaria.

Brimonidine Tartrate 0.2%

In clinical studies of brimonidine tartrate 0.2%, adverse reactions occurring in approximately 10 to 30% of the subjects, in descending order of incidence, included oral dryness, ocular hyperemia, burning and stinging, headache, blurring, foreign body sensation, fatigue/drowsiness, conjunctival follicles, ocular allergic reactions, and ocular pruritus.

Reactions occurring in approximately 3 to 9% of the subjects, in descending order included corneal staining/erosion, photophobia, eyelid erythema, ocular ache/pain, ocular dryness, tearing, upper respiratory symptoms, eyelid edema, conjunctival edema, dizziness, blepharitis, ocular irritation, gastrointestinal symptoms, asthenia, conjunctival blanching, abnormal vision and muscular pain.

The following adverse reactions were reported in less than 3% of the patients: lid crusting, conjunctival hemorrhage, abnormal taste, insomnia, conjunctival discharge, depression, hypertension, anxiety, palpitations/arrhythmias, nasal dryness and syncope.

6.2 Postmarketing Experience

The following reactions have been identified during postmarketing use of brimonidine tartrate ophthalmic solutions in clinical practice. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. The reactions, which have been chosen for inclusion due to either their seriousness, frequency of reporting, possible causal connection to brimonidine tartrate ophthalmic solutions, or a combination of these factors, include: bradycardia, hypersensitivity, iritis, keratoconjunctivitis sicca, miosis, nausea, skin reactions (including erythema, eyelid pruritus, rash, and vasodilation), and tachycardia.

Apnea, bradycardia, coma, hypotension, hypothermia, hypotonia, lethargy, pallor, respiratory depression, and somnolence have been reported in infants receiving brimonidine tartrate ophthalmic solutions *[see Contraindications (4.3)]*.

7 DRUG INTERACTIONS

7.1 Oral Carbonic Anhydrase Inhibitors

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 brinzolamide ophthalmic suspension 1%, a component of SIMBRINZA™. The concomitant administration of SIMBRINZA™ and oral carbonic anhydrase inhibitors is not recommended.

7.2 High-Dose Salicylate Therapy

Carbonic anhydrase inhibitors may produce acid-base and electrolyte alterations. These alterations were not reported in the clinical trials with brinzolamide ophthalmic suspension 1%. However, in patients treated with oral carbonic anhydrase inhibitors, rare instances of acid-base alterations have occurred with high-dose salicylate therapy. Therefore, the potential for such drug interactions should be considered in patients receiving SIMBRINZA™.

7.3 CNS Depressants

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

7.4 Antihypertensives/Cardiac Glycosides

Because brimonidine tartrate, a component of SIMBRINZA™, may reduce blood pressure, caution in using drugs such as antihypertensives and/or cardiac glycosides with SIMBRINZA™ is advised.

7.5 Tricyclic Antidepressants

Tricyclic antidepressants have been reported to blunt the hypotensive effect of systemic clonidine. It is not known whether the concurrent use of these agents with SIMBRINZA™ in humans can lead to resulting interference with the IOP lowering effect. Caution is advised in patients taking tricyclic antidepressants which can affect the metabolism and uptake of circulating amines.

7.6 Monoamine Oxidase Inhibitors

Monoamine oxidase (MAO) inhibitors may theoretically interfere with the metabolism of brimonidine tartrate and potentially result in an increased systemic side-effect such as hypotension. Caution is advised in patients taking MAO inhibitors which can affect the metabolism and uptake of circulating amines.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C: Developmental toxicity studies with brinzolamide in rabbits at oral doses of 1, 3, and 6 mg/kg/day (20, 60, and 120 times the recommended human ophthalmic dose)

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