targeting elevated IOP

Opening up possibilities for the reduction of elevated IOP in patients with open-angle glaucoma or ocular hypertension with fixed-combination therapy.

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REVIEW® OF OPTOMETRY

targeting elevated IOP with

SIMBRINZA® (brinzolamide/brimonidine tartrate ophthalmic suspension) 1%/0.2%

Opening up possibilities for the reduction of elevated IOP in patients with open-angle glaucoma or ocular hypertension with fixed-combination therapy.

PARTICIPANTS

- *(Moderator)* **Murray Fingeret, OD**, is chief of the Optometry Section, Brooklyn/St. Albans Campus, Department of Veterans Administration New York Harbor Health Care System, and clinical professor at the State University of New York College of Optometry. Dr. Fingeret is also a paid consultant for Alcon.
- **I. Ben Gaddie, OD,** is director of Gaddie Eye Centers in Louisville, Ky., and is president of the Optometric Glaucoma Society. Dr. Gaddie also serves as a paid consultant for Alcon.
- **Richard J. Madonna, OD,** is a professor at the State University of New York College of Optometry, as well as chairman of the Department of Clinical Education. Dr. Madonna is also a paid consultant for Alcon.

All participants were paid by Alcon for their contributions to this project.

SIMBRINZA® Suspension Important Information

Indications and Usage

SIMBRINZA® (brinzolamide/brimonidine tartrate ophthalmic suspension) 1%/0.2% is a fixed combination indicated in the reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension.

Dosage and Administration

The recommended dose is one drop of SIMBRINZA® Suspension in the affected eye(s) three times daily. Shake well before use. SIMBRINZA® 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.

Elevated intraocular pressure (IOP) is a major risk factor for glaucoma; thus, individuals with ocular hypertension (OHT) are considered to have a greater chance of developing the condition. The primary standard therapy in patients with open-angle glaucoma or ocular hypertension is topical medication to lower IOP. Typically, patients are treated with a single medication at the onset of treatment, so called monotherapy. Many times, monotherapy doesn't achieve target IOP. That's when doctors will prescribe additional products as adjunctive therapy.

Three highly respected thought leaders gathered at a recent industry meeting to talk about a fixed-combination treatment for elevated IOP, SIMBRINZA® (brinzolamide/brimonidine tartrate ophthalmic suspension 1%/0.2%, Alcon). The following monograph outlines their discussion, which includes the drug's indications, warnings and precautions associated with it, results of pivotal Phase III trials and more.

SIMBRINZA® Suspension Up Close & Personal

Murray Fingeret, OD: What is SIMBRINZA® Suspension?

Richard Madonna, OD: SIMBRINZA® Suspension is a fixed-dose combination of two medications that we already know: brinzolamide 1% and brimonidine 0.2%.

Dr. Fingeret: Why is there a need for a fixed combination such as SIMBRINZA® Suspension when treating patients who have open-angle glaucoma (OAG)?

I. Ben Gaddie, OD: The longer you treat patients with OAG, the more common it's going to be to need more than one medication. In fact, nearly 40% of all patients being treated require more than one medication to lower intraocular pressure (IOP) after five years.[1] Using a fixed combination results in one co-pay for the patient because these are two drugs in one bottle. It's also nice to have a fixed-combination medication option that does not contain a beta-blocker.

Dr. Fingeret: What type of patient is SIMBRINZA® Suspension indicated for? And how should it be used?

Dr. Madonna: SIMBRINZA® Suspension is a fixed combination indicated for the reduction of IOP in patients with OAG or ocular hypertension. Let's think about how we're going to utilize it in our patients. The recommended dosage is one drop of the suspension in the affected eye three times daily. Because this drug is a suspension, we have to tell our patients to shake the bottle well before they use it. And, many times, we're treating our patients with more than one drop. If more than one topical ophthalmic drug is being used, the drugs should be administered at least five (5) minutes apart. We're always concerned, of course, about washout.

Contraindications to SIMBRINZA® Suspension include patients who are hypersensitive to any component of the product and in neonates and infants under the age of two years.[2]

Dr. Fingeret: Thank you, Dr. Madonna. Can you describe the mechanism of action (MOA) for SIMBRINZA® Suspension and explain how is it a different fixed combination?

How It Works & Why It's Different

Dr. Madonna: First, let's again look at the two individual components of this drug. We know that brinzolamide is a carbonic anhydrase inhibitor (CAI) that reduces aqueous production, whereas brimonidine—an alpha 2 adrenergic receptor agonist—also reduces aqueous production, but additionally increases uveoscleral outflow. Therefore, SIMBRINZA® Suspension has two active compounds with different MOAs.[2]

SIMBRINZA® *Suspension Important Safety Information*

Important Safety Information

Contraindications

SIMBRINZA® Suspension is contraindicated in patients who are hypersensitive to any component of this product and neonates and infants under the age of 2 years.

Warnings and Precautions

Sulfonamide Hypersensitivity Reactions—Brinzolamide is a sulfonamide, and although administered topically, is absorbed systemically. Sulfonamide attributable adverse reactions may occur. Fatalities have occurred due to severe reactions to sulfonamides. Sensitization may recur when a sulfonamide is readministered irrespective of the route of administration. If signs of serious reactions or hypersensitivity occur, discontinue the use of this preparation.

Corneal Endothelium—There is an increased potential for developing corneal edema in patients with low endothelial cell counts.

Severe Hepatic or Renal Impairment (CrCl <30 mL/min)—SIMBRINZA® Suspension has not been specifically studied in these patients and is not recommended.

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

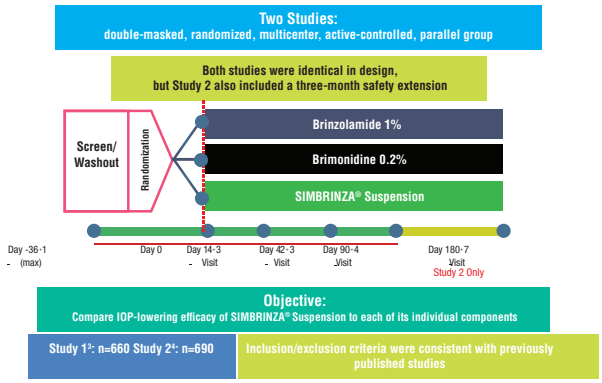

Figure 1. Breakdown of two peer-reviewed publications from pivotal FDA trials.

Dr. Gaddie: And as far as how it's a different fixed combination, it's the only available combination that is beta-blocker-free.[3,4]

Dr. Fingeret: Great, that's all very important to know about this drug. Clinical data are also useful. What does the clinical data on SIMBRINZA® (brinzolamide/brimonidine tartrate ophthalmic suspension) 1%/0.2% say?

Sifting Through the Clinical Data

Dr. Gaddie: The data from the SIMBRINZA® Suspension registration trials have been published in two peer-reviewed publications.

The objective of these two clinical studies was to compare the IOP-lowering efficacy of SIMBRINZA® Suspension to each of its individual components and to demonstrate the superiority of the SIMBRINZA® Suspension fixed-combination over brinzolamide alone and brimonidine alone (see Figure 1). Both studies were double-masked, randomized, multicenter, active-controlled and parallel group studies. Study One enrolled 660 patients, with the intent-to-treat (ITT) population totalling 649 and 594 patients completing this study.[3] Study Two enrolled 690 patients with the ITT population totalling 679 and 615 patients completing the study.[4] Both studies were identical in design and ran for a total of 90 days; however, Study Two included an additional three-month safety extension to look at any other safety types of concerns, but this will not be presented here.

In both studies, patients were screened against the inclusion and exclusion criteria and washed out of their current IOP-lowering medications (five days for miotics and oral/topical CAIs,14 days for alpha-agonists and alpha/beta-agonists, and 28 days for beta-blockers and prostaglandin analogs). Following the washout period, IOP was measured at two eligibility visits spaced three to eight days apart. At both eligibility visits, patients were required to have a mean IOP of 24mm Hg to 36mm Hg at 8 a.m. and 21mm Hg to 36mm Hg at 10 a.m. The stratified groups were then randomized 1:1:1 to treatment with SIMBRINZA® Suspension, brinzolamide 1% or brimonidine 0.2%. The dosing regimen was one drop in each eye t.i.d.

Between the two trials, more than 1,300 patients were studied and the inclusion/exclusion criteria were consistent with other registration or pivotal type of trials. The objective really was to demonstrate that SIMBRINZA® Suspension had greater efficacy at lowering IOP compared to each of the two individual components alone.

Dr. Madonna: The endpoint in the trial was the mean IOP at Month Three for all time points: 8 a.m., 10 a.m.,3 p.m. and 5 p.m. Dosing of the medications were 8 a.m., 3 p.m. and 10 p.m. (see Figure 2).

Dr. Gaddie: Keep in mind that the IOP was measured prior to the dosing of the medication at those times.

Dr. Fingeret: Mean IOP was also measured at week two and week six for all the different time points.

Now that we've reviewed the components, MOA and clini-

SIMBRINZA® Suspension Provided Additional 1–3mm Hg IOP-lowering Compared to the Individual Components

	Brinzolamide 1%	Brimonidine 0.2%
Study 1[3]		
Month 3	Difference (95% CI)*	Difference (95% CI)*
8 a.m.	-1.1 (-1.8, -0.4)	-2.8 (-3.5, -2.1)
10 a.m.	-3.2 (-3.9, -2.5)	-2.5 (-3.2, -1.8)
3 p.m.	-1.8 (-2.5, -1.1)	-2.6 (-3.3, -1.9)
5 p.m.	-3.0 (-3.7, -2.3)	-1.8 (-2.5, -1.1)
Study 2[4]		
Month 3	Difference (95% CI)*	Difference (95% CI)*
8 a.m.	-1.0 (-1.7, -0.3)	-2.2 (-2.9, -1.5)
10 a.m.	-2.8 (-3.5, -2.1)	-1.9 (-2.6, -1.2)
3 p.m.	-1.2 (-1.9, -0.5)	-2.0 (-2.7, -1.3)
5 p.m.	-3.2 (-3.9, -2.5)	-1.7 (-2.4, -1.0)

Figure 2. SIMBRINZA® (brinzolamide/brimonidine tartrate ophthalmic suspension) 1%/0.2% provided an additional 1mm Hg to 3mm Hg IOP lowering compared to the individual components. *Mean IOP (mm Hg) treatment difference by treatment group compared to SIMBRINZA® Suspension at the primary endpoint (Month 3).

SIMBRINZA® *Suspension Important Safety Information, cont'd.*

Contact Lens Wear—The preservative in SIMBRINZA® Suspension, benzalkonium chloride, may be absorbed by soft contact lenses. Contact lenses should be removed during instillation of SIMBRINZA® Suspension but may be reinserted 15 minutes after instillation.

Severe Cardiovascular Disease—Brimonidine tartrate, a component of SIMBRINZA® Suspension, had 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.

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

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 inadver-

cal data on SIMBRINZA® (brinzolamide/brimonidine tartrate ophthalmic suspension) 1%/0.2%, what do we feel we can expect from this drug in terms of IOP-lowering efficacy?

Defining Expectations

Dr. Madonna: This is exciting because these studies clearly indicate that we can expect from 1mm Hg to 3mm Hg effective IOP lowering compared to the individual components, and 5.4mm Hg to 8.8mm Hg IOP reduction from baseline.[3,4] This equates to delivering about 21% to 35% IOP-lowering efficacy, so it's very exciting what this medication can provide.

Dr. Gaddie: To take this a little further, if you look at the data in Figure 3, you see the efficacy of SIMBRINZA® Suspension at all time points was superior to the individual components of brinzolamide or brimonidine.[2-4]

Dr. Fingeret: Right, and Study Two demonstrated results similar to Study One.

Safety Precautions

Dr. Fingeret: Dr. Gaddie, based on the Phase III trials, describe the safety profile.

Dr. Gaddie: As we mentioned earlier, there were no additional risks of SIMBRINZA® Suspension versus those in the individual components. Both are well-known components that we've used clinically for years, and I think SIMBRINZA® Suspension's side effect profile really mirrors the side effects of the two individual components.

Dr. Fingeret: Thank you, Dr. Gaddie. That leads us to our next topic: the warnings and precautions associated with SIMBRINZA® Suspension. Who can review these for us?

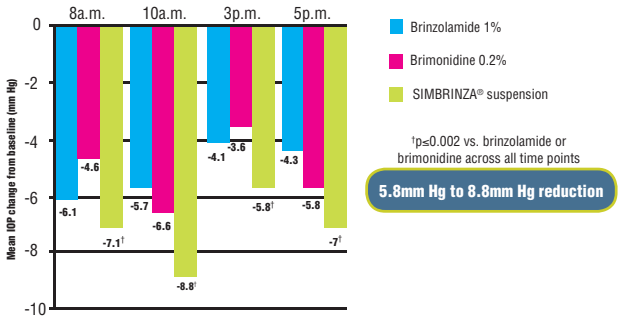

Figure 3. Intraocular pressure control at all timepoints at month three in Study One.[3]

Dr. Gaddie: We really have a few main categories about which to be concerned.

SIMBRINZA® Suspension 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® Suspension. 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. If signs of serious reactions or hypersensitivity occur, discontinue the use of this preparation.

SIMBRINZA® Suspension should be used with caution in patients with low endothelial cell counts because the topical CAI component can cause corneal edema.

Additionally, SIMBRINZA® Suspension has not been specifically studied in patients with severe renal impairment (CrCl <30 mL/min). Because brinzolamide and its metabolite are excreted predominantly by the kidney, SIMBRINZA® Suspension is not recommended in such patients.

Dr. Madonna: Dr. Gaddie, I agree with you 100% about patients with sulfa allergies. We should also exercise caution in other areas when prescribing SIMBRINZA® Suspension.

For example, we obviously know that not all glaucoma is primary open-angle glaucoma (POAG) or ocular hypertension. The management of patients with acute angle-closure glaucoma requires therapeutic interventions in addition to ocular hypotensive agents. It's important to note that SIMBRINZA® Suspension has not been studied in patients with acute angle-closure glaucoma.

Some of our patients may be contact lens wearers, so we must remember that the preservative in SIMBRINZA® Suspension is benzalkonium chloride (BAK), which may be absorbed by soft contact lenses. Therefore, patients should be told to remove their lenses during instillation of SIMBRINZA® Suspension. They may re-insert them 15 minutes later.

The brimonidine component of SIMBRINZA® Suspension has been shown to have a less than 5% mean decrease in blood pressure two hours after dosing. Caution should be exercised in treating patients with severe cardiovascular disease.

Because brimonidine tartrate, a component of SIMBRINZA® Suspension, has not been studied in patients with hepatic impairment, caution should be exercised in such patients.

Dr. Fingeret: Excellent points. There's also the potentiation of vascular insufficiency.[2] Brimonidine tartrate, a component

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SIMBRINZA® *Suspension Important Safety Information, cont'd.*

tently contaminated by patients who, in most cases, had a concurrent corneal disease or a disruption of the ocular epithelial surface.

Adverse Reactions
SIMBRINZA® Suspension

In two clinical trials of 3 months' duration with SIMBRINZA® Suspension, the most frequent reactions associated with its use occurring in approximately 3-5% of patients in descending order of incidence included: blurred vision, eye irritation, dysgeusia (bad taste), dry mouth, and eye allergy. Adverse reaction rates with SIMBRINZA® Suspension were comparable to those of the individual components. Treatment discontinuation, mainly due to adverse reactions, was reported in 11% of SIMBRINZA® Suspension patients.

Brinzolamide 1%

In clinical studies of brinzolamide ophthalmic suspension 1%, the most frequently reported adverse events reported in 5-10% of patients were blurred vision and bitter, sour, or

Adverse Events Associated with SIMBRINZA® (brinzolamide/brimonidine tartrate ophthalmic suspension) 1%/0.2% in the Pivotal Phase III Trials

- The most frequently reported adverse reactions in a six-month clinical trial in patients treated with SIMBRINZA® Suspension occurring in approximately 3% to 7% of patients in descending order of incidence were eye irritation (6.3%), eye allergy (6.3%), conjunctivitis (5.0%), blurred vision (4.5%), dysgeusia (bad taste, 4.1%), conjunctivitis allergic (3.6%), eye pruritus (3.2%) and dry mouth (3.2%).
- Treatment discontinuation, mainly due to adverse reactions, was reported in 17.2% of SIMBRINZA® Suspension patients.
- There were no significant cardiovascular or pulmonary events found with SIMBRINZA® Suspension in either clinical study conducted.[3,4*]

** Caution should be exercised when treating patients with «severe cardiovascular disease.*

of SIMBRINZA® Suspension, may potentiate syndromes associated with vascular insufficiency and thus, should be used with caution in patients who are depressed or have cerebral or coronary insufficiency, Raynaud's phenomenon, orthostatic hypotension or thromboangitis obliterans.

We also need to be careful about contamination of topical ophthalmic products after use. The use of local multiple-dose containers of topical ophthalmic products may result in an increased risk of ocular infection. These containers can be inadvertently contaminated by patients who have a concurrent corneal disease or disruption of the ocular epithelial surface.

Dr. Madonna, can you discuss the adverse reactions associated with SIMBRINZA® Suspension in the pivotal Phase III trials?

Adverse Reactions

Dr. Madonna: No additional risks were identified with SIMBRINZA® Suspension compared to those observed with the individual components (brinzolamide and brimonidine). However, this is not surprising, as the adverse events profile of each component has been well established. The most frequently reported adverse reactions in a six-month clinical trial in patients treated with SIMBRINZA® Suspension occurring in approximately 3% to 7% of patients in descending order of incidence were eye irritation (6.3%), eye allergy (6.3%), conjunctivitis (5.0%), blurred vision (4.5%), dysgeusia (bad taste, 4.1%), conjunctivitis allergic (3.6%), eye pruritus (3.2%), and dry mouth (3.2%). Treatment discontinuation, mainly due to adverse reactions, was reported in 17.2% of SIMBRINZA® Suspension patients.[5] Finally, there were no significant cardiovascular or pulmonary events observed with SIMBRINZA® Suspension.[3,4] Again, caution should be exercised when treating patients with severe cardiovascular disease.

Dr. Gaddie: It's also important to point out that the adverse events that Dr. Madonna just described can be attributable to each of the drug's individual components: brinzolamide and brimonidine.

Dr. Fingeret: How would you summarize what we have with SIMBRINZA® Suspension?

SIMBRINZA® Suspension in a Nutshell

Dr. Madonna: First and foremost, we get an additional 1mm Hg to 3mm Hg of IOP-lowering with SIMBRINZA® Suspension compared to individual components.[2-4] Second, it delivers about 21% to 35% IOP-lowering efficacy vs. baseline. It's also the only fixed combination that doesn't contain a beta-blocker, and as Dr. Gaddie just said, the adverse events profile is consistent with those of the individual components, so there's no surprises.[2-4] Overall, I believe that SIMBRINZA® Suspension creates treatment possibilities for lowering IOP for any of us who treat a lot of OAG.

Dr. Fingeret: Thank you, Dr. Madonna. Next, let's talk about some patient scenarios in which we may use SIMBRINZA® Suspension. Dr. Gaddie, would you start us off?

Patient Possibilities for SIMBRINZA® Suspension

Dr. Gaddie: Sure. I think probably the most obvious utilization for SIMBRINZA® Suspension would be a patient who is not at target pressure on the primary therapy of a prostaglandin. We see this all the time, and traditionally, our options are then to add a single component such as brinzolamide or brimonidine, or to go straight to a combination. So now, if we want to add an additional medication to a PGA, we have the option to move straight to SIMBRINZA® Suspension.

Dr. Fingeret: Another scenario may be in a patient

SIMBRINZA® *Suspension Important Safety Information, cont'd.*

unusual taste. Adverse events occurring in 1-5% of patients were blepharitis, dermatitis, dry eye, foreign body sensation, headache, hyperemia, ocular discharge, ocular discomfort, ocular keratitis, ocular pain, ocular pruritus, and rhinitis.

Brimonidine Tartrate 0.2%

In clinical studies of brimonidine tartrate 0.2%, adverse events occurring in approximately 10-30% 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.

Events occurring in approximately 3-9% 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.

who is on a systemic beta-blocker and a topical prostaglandin analog, but you want to add another medication. SIMBRINZA® (brinzolamide/brimonidine tartrate ophthalmic suspension) 1%/0.2% would be an option to consider adding in this instance.

Dr. Gaddie: And the most common situation we'll see ourselves in is with a patient on either brinzolamide or brimonidine who needs additional IOP-lowering, in which case it is necessary to move straight to the combination.

Dr. Fingeret: SIMBRINZA® Suspension may also be a good fit in a monotherapy situation with a new patient. Prostaglandins may not an option for every patient, SIMBRINZA® Suspension may be an alternative in that case.

Dr. Gaddie: Interestingly, another important scenario is in patients who only need treatment in one eye.

SIMBRINZA® Suspension may also be an option to patients who have cardiovascular and cardiopulmonary disorders such as chronic obstructive pulmonary disease and asthma and who are already on a prostaglandin and in need of additional medication. Caution should be used when treating patients with severe cardiovascular disease.

Dr. Fingeret: Thank you, doctors. I think we have covered some very useful information in this discussion.

SIMBRINZA® Suspension opens up possibilities in lowering IOP in patients with OAG or ocular hypertension. We hope the information we have shared here proves useful to you when managing your own patients.

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CASE STUDIES

Richard Madonna, OD

I recently used SIMBRINZA® Suspension in two patients, which I describe in the cases below.

• **A 46-year-old black woman** with a 14-year history of open-angle glaucoma (OAG) also had high myopia and a significant medical history of asthma. She has advanced cupping and moderate visual field loss, with the field in the right eye showing some early signs of progression. Her highest measured untreated intraocular pressures (IOPs) were 28mm Hg in her right eye and 22mm Hg in the left. She has been treated medically for a number of years along with having argon laser trabeculoplasty performed in each eye.

What is really significant about this patient is her history of poor adherence to the follow-up and medication, although this has improved to some degree over time. When I last saw her, she was being treated with latanoprost, brinzolamide ophthalmic suspension 1% and brimonidine tartrate ophthalmic solution 0.1%. Her IOPs were 17mm Hg (OD) and 14mm Hg (OS). She had been taking five drops in each eye per day. I switched this patient to SIMBRINZA® Suspension, reducing the number of drops she needed to instill each day.

• **A 64-year-old man** with a history of primary OAG presented as a new patient to me. He wasn't sure how long he had been treated, but he was taking a prostaglandin once per day in both eyes and had pressures of 15mm Hg OU. He had cataract surgery in his right eye, but developed cystoid macular edema in that eye, so we decided to not keep him on the prostaglandin analog. We then initiated treatment with SIMBRINZA® Suspension three times a day.

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SIMBRINZA® *Suspension Important Safety Information, cont'd.*

Drug Interactions—Consider the following when prescribing SIMBRINZA® Suspension:

Concomitant administration with oral carbonic anhydrase inhibitors is not recommended due to the potential additive effect. Use with high-dose salicylate may result in acid-base and electrolyte alterations. Use with CNS depressants may result in an additive or potentiating effect. Use with antihypertensives/cardiac glycosides may result in additive or potentiating effect on lowering blood pressure. Use with tricyclic antidepressants may blunt the hypotensive effect of systemic clonidine and it is unknown if use with this class of drugs interferes with IOP lowering. Use with monoamine oxidase inhibitors may result in increased hypotension.

For additional information about SIMBRINZA® Suspension, please see the brief summary of Prescribing Information.

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BRIEF SUMMARY OF PRESCRIBING INFORMATION
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.

DOSAGE AND ADMINISTRATION

The recommended dose is one drop of SIMBRINZA™ Suspension in the affected eye(s) three times daily. Shake well before use. SIMBRINZA™ 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.

DOSAGE FORMS AND STRENGTHS

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

CONTRAINDICATIONS

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

Neonates and Infants (under the age of 2 years) - SIMBRINZA™ Suspension is contraindicated in neonates and infants (under the age of 2 years*) see Use in Specific Populations*

WARNINGS AND PRECAUTIONS

Sulfonamide Hypersensitivity Reactions - SIMBRINZA™ Suspension 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™ Suspension. 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]*

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™ Suspension to this group of patients.

Severe Renal Impairment - SIMBRINZA™ Suspension 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™ Suspension is not recommended in such patients.

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

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™ Suspension but may be reinserted 15 minutes after instillation *[see Patient Counseling Information]*.

Severe Cardiovascular Disease - Brimonidine tartrate, a component of SIMBRINZA™ Suspension, 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.

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

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

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]*.

ADVERSE REACTIONS

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™ Suspension - In two clinical trials of 3 months duration 435 patients were treated with SIMBRINZA™ Suspension, and 915 were treated with the two individual components. The most frequently reported adverse reactions in patients treated with SIMBRINZA™ Suspension 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™ Suspension 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.

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]*.

DRUG INTERACTIONS

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

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™ Suspension.

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.

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

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™ Suspension 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.

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.

USE IN SPECIFIC POPULATIONS

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) produced maternal toxicity at 6 mg/kg/day and a significant increase in the number of fetal variations, such as accessory skull bones, which was only slightly higher than the historic value at 1 and 6 mg/kg. In rats, statistically decreased body weights of fetuses from dams receiving oral doses of 18 mg/kg/day (180 times the recommended human ophthalmic dose) during gestation were proportional to the reduced maternal weight gain, with no statistically significant effects on organ or tissue development. Increases in unossified sternebrae, reduced ossification of the skull, and unossified hyoid that occurred at 6 and 18 mg/kg were not statistically significant. No treatment-related malformations were seen. Following oral administration of ^{14}C-brinzolamide to pregnant rats, radioactivity was found to cross the placenta and was present in the fetal tissues and blood.

Developmental toxicity studies performed in rats with oral doses of 0.66 mg brimonidine base/kg revealed no evidence of harm to the fetus. Dosing at this level resulted in a plasma drug concentration approximately 100 times higher than that seen in humans at the recommended human ophthalmic dose. In animal studies, brimonidine crossed the placenta and entered into the fetal circulation to a limited extent.

There are no adequate and well-controlled studies in pregnant women. SIMBRINZA™ Suspension should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers - In a study of brinzolamide in lactating rats, decreases in body weight gain in offspring at an oral dose of 15 mg/kg/day (150 times the recommended human ophthalmic dose) were observed during lactation. No other effects were observed. However, following oral administration of ^{14}C-brinzolamide to lactating rats, radioactivity was found in milk at concentrations below those in the blood and plasma. In animal studies, brimonidine was excreted in breast milk.

It is not known whether brinzolamide and brimonidine tartrate are excreted in human milk following topical ocular administration. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from SIMBRINZA™ (brinzolamide/brimonidine tartrate ophthalmic suspension) 1%/0.2%, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use - The individual component, brinzolamide, has been studied in pediatric glaucoma patients 4 weeks to 5 years of age. The individual component, brimonidine tartrate, has been studied in pediatric patients 2 to 7 years old. Somnolence (50-83%) and decreased alertness was seen in patients 2 to 6 years old. SIMBRINZA™ Suspension is contraindicated in children under the age of 2 years *[see Contraindications]*.

Geriatric Use - No overall differences in safety or effectiveness have been observed between elderly and adult patients.

OVERDOSAGE

Although no human data are available, electrolyte imbalance, development of an acidotic state, and possible nervous system effects may occur following an oral overdose of brinzolamide. Serum electrolyte levels (particularly potassium) and blood pH levels should be monitored.

Very limited information exists on accidental ingestion of brimonidine in adults; the only adverse event reported to date has been hypotension. Symptoms of brimonidine overdose have been reported in neonates, infants, and children receiving brimonidine as part of medical treatment of congenital glaucoma or by accidental oral ingestion. Treatment of an oral overdose includes supportive and symptomatic therapy; a patent airway should be maintained.

PATIENT COUNSELING INFORMATION

Sulfonamide Reactions - Advise patients that if serious or unusual ocular or systemic reactions or signs of hypersensitivity occur, they should discontinue the use of the product and consult their physician.

Temporary Blurred Vision - Vision may be temporarily blurred following dosing with SIMBRINZA™ Suspension. Care should be exercised in operating machinery or driving a motor vehicle.

Effect on Ability to Drive and Use Machinery - As with other drugs in this class, SIMBRINZA™ Suspension may cause fatigue and/or drowsiness in some patients. Caution patients who engage in hazardous activities of the potential for a decrease in mental alertness.

Avoiding Contamination of the Product - Instruct patients that ocular solutions, if handled improperly or if the tip of the dispensing container contacts the eye or surrounding structures, can become contaminated by common bacteria known to cause ocular infections. Serious damage to the eye and subsequent loss of vision may result from using contaminated solutions *[see Warnings and Precautions]*. Always replace the cap after using. If solution changes color or becomes cloudy, do not use. Do not use the product after the expiration date marked on the bottle.

Intercurrent Ocular Conditions - Advise patients that if they have ocular surgery or develop an intercurrent ocular condition (e.g., trauma or infection), they should immediately seek their physician's advice concerning the continued use of the present multidose container.

Concomitant Topical Ocular Therapy - If more than one topical ophthalmic drug is being used, the drugs should be administered at least five minutes apart.

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™ Suspension, but may be reinserted 15 minutes after instillation.

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