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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targeting elevated IOP
with SIMBRINZA® (brinzolamide/brimonidine tartrate ophthalmic suspension) 1%/0.2%

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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
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, parallel group studies. Study One enrolled 660 patients, with the intent-to-treat (ITT) population totaling 649 and 594 patients completing this study. Study Two enrolled 690 patients with the ITT population totaling 679 and 615 patients completing the study. 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/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 clinical results, we can review the efficacy of SIMBRINZA® Suspension.

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

**Figure 2.** SIMBRINZA® (brinzolamide/brimonidine tartrate ophthalmic suspension) 1%/0.2% provided an additional 1–3mm Hg IOP-lowering Compared to the Individual Components.
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. 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?

**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 (Ccr <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...
However, this is not surprising, as the adverse events profile of each component has been well established. The most frequent adverse events 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. 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 thromboangiitis 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.

There were no significant cardiovascular or pulmonary events found with SIMBRINZA® Suspension in either clinical study conducted. Caution should be exercised when treating patients with severe cardiovascular disease.

SIMBRINZA® Suspension in a Nutshell
Dr. Madonna: First and foremost, we get an additional 1 mm Hg to 3 mm Hg of IOP-lowering with SIMBRINZA® Suspension compared to individual components. 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 in a patient scenarios in which we may use SIMBRINZA® Suspension in the pivotal Phase III trials.

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

- The most frequently reported adverse reaction 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. 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?
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.

**REFERENCES**


2. SIMBRINZA® Suspension Package Insert.


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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 trabeculectomy 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® Suspensionthree times a day.

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

**DOSAGE AND ADMINISTRATION**

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

**DOSE FORMS AND STRENGTHS**

- Brinzolamide 1%/0.2%: 1 mg, brinzolamide 2 mg, brimonidine tartrate.

**CONTRAINDICATIONS**

- Hypersensitivity - SIMBRINZA™ Suspension is contraindicated in patients who are hypersensitive to any component of this product.
- Neovascular (vanguard) glaucoma - SIMBRINZA™ Suspension is contraindicated in patients under the age of 2 years [see Use in Specific Populations]

**WARNINGS AND PRECAUTIONS**

**Drug Interactions**

- Monoamine Oxidase Inhibitors - Caution is advised in patients taking MAO inhibitors as the potential for drug interactions may theoretically interfere with the metabolism of brimonidine tartrate and result in an increase in IOP.
- Tricyclic antidepressants have been reported to result in an increase in pressure. Caution is advised in patients taking tricyclic antidepressants and those with a history of cardiovascular disease.
- Potentiation of Vascular Insufficiency - Direct ophthalmoscopic examination should be performed prior to therapy. Caution should be exercised in patients with a history of cardiovascular disease.
- Potentially life-threatening adverse events including serious cardiovascular events and cardiac arrest, have been reports of death in patients with cardiovascular disease.

**OVERDOSAGE**

- 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. Dosing at this level resulted in a plasma drug concentration approximately 100 times higher than that seen in humans at the recommended daily human ophthalmic dose. In animal studies, brinzolamide crossed the placenta and entered into the fetal circulation to a limited extent.

**REFERENCES**

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