Glaucoma affects an estimated 2.2 million people in the United States, and is estimated to affect as many as 3 million people by 2020. Its prevalence is projected to rise with the aging of the US population. Glaucoma has the potential to destroy retinal ganglion cells in the optic nerve, which can lead to severe vision loss and blindness. In fact, glaucoma is a leading cause of blindness in the United States, accounting for 9% to 12% of all cases of blindness. 

The 2 main types of glaucoma are open-angle glaucoma and angle-closure glaucoma. Open-angle glaucoma, also referred to as primary or chronic glaucoma, is the most common type, accounting for ≥90% of all cases of glaucoma. People aged ≥60 years are at an increased risk for glaucoma, particularly in the Hispanic population. The risk for open-angle glaucoma increases at age ≥40 years. African Americans are 15 times more likely to have glaucoma-related visual impairment than Caucasians.

Patients with glaucoma often have increased intraocular pressure (IOP)—a condition that may prevent retinal ganglion cells from receiving a brain-derived neurotrophic factor (a protein required for retinal ganglion cell survival) from nearby cells in the optic nerve. An estimated 70% of patients with glaucoma have a history of elevated IOP. An elevated baseline IOP is one of the only modifiable risk factors associated with open-angle glaucoma. Other potentially modifiable factors, including IOP fluctuation and nutrition, are also being studied.

Ocular hypertension is characterized by an IOP of >21 mm Hg, the upper limit of normal IOP in the general population. According to several population studies, an estimated 4% to 10% of people aged ≥40 years will have an IOP of ≥21 mm Hg without detectable signs of damage from glaucoma.

Glaucoma imposes a substantial burden on a person’s quality of life, affecting driving, walking, and reading, and it may also lead to social withdrawal and depression. Vision loss has a dramatic societal and economic impact, because it may result in disability, suffering, and loss of productivity. Glaucoma accounts for an estimated $2.9 billion in direct costs annually in the United States. These costs may actually be higher than currently estimated, given that many people with glaucoma are unaware that they have the condition. Furthermore, the financial burden of glaucoma increases with the severity of the disease.

Glaucoma is an underdiagnosed condition that has a profound need for earlier diagnosis, which can help to slow its progression and improve patient outcomes. Glaucoma is often undiagnosed because it is relatively asymptomatic, particularly in the early stages, and a person may not seek medical attention until loss of vision occurs. In addition, many patients with diagnosed glaucoma are either not receiving treatment or their treatment is delayed. Proactive, early management can reduce the overall disease burden of glaucoma, and potentially its economic burden as well.

Management of Open-Angle Glaucoma and Ocular Hypertension: Challenges and Opportunities

The Early Manifest Glaucoma Trial, a 6-year collaborative study, confirmed the accumulating medical evidence showing that reducing eye pressure in the early stages of glaucoma slowed the progression of the disease. Another major study, the Ocular Hypertension Treatment Study (N = 1636), showed that topical ocular hypotensive therapy delayed or prevented the onset of primary open-angle glaucoma in patients with an elevated IOP, thereby reducing the development of glaucoma by more than 50%. A follow-up study of the Ocular Hypertension Treatment Study (N = 203) demonstrated that the use of daily topical ocular hypotensive therapy reduced the development of primary open-angle glaucoma in African-American patients by nearly 50%.

The key therapeutic goal for glaucoma is to manage or to reduce IOP to mitigate the likelihood of optic nerve damage. Overall in the United States, pharmacologic treatment (with an ophthalmic solution) is the primary treatment choice, or a combination of medication and laser treatment. Pharmacologic treatments include several drug classes, such as prostaglandin analogs, beta-blockers, alpha agonists, carbonic anhydrase inhibitors, miotics, and combination medications.
Medications for the treatment of glaucoma are associated with class-specific adverse events; however, the incidence of these side effects may vary from one agent to another. Moreover, some patients may be allergic or be sensitive to preservatives used in ophthalmic agents.12 When monitoring or treating patients, it may be challenging for clinicians to find an IOP range that helps to stabilize the patient’s visual fields and optic nerve and/or retinal nerve fiber status.13

Inadequate medication adherence is often another barrier to the optimal management of glaucoma, particularly when patients forget to administer their prescribed eye drops.12,13 A patient’s failure to follow the prescribed therapeutic regimen can result in serious consequences, including continued optic neuropathy and vision loss.13 Comorbid conditions (eg, diabetes, hypertension, hyperlipidemia) and associated polypharmacy may also have an impact on medication adherence.13

Simbrinza: Fixed-Dose Combination Indicated for Reduction of Intraocular Pressure

On April 19, 2013, the US Food and Drug Administration (FDA) approved brinzolamide 1%/brimonidine tartrate 0.2% ophthalmic suspension (Simbrinza; Alcon Laboratories) for the reduction of elevated IOP in patients with primary open-angle glaucoma or ocular hypertension.14 Brinzolamide 1% plus brimonidine tartrate 0.2% is a fixed-dose combination of a carbonic anhydrase inhibitor and an alpha-2 adrenergic receptor agonist that is indicated for the reduction of elevated IOP.14 Brinzolamide/brimonidine is currently the only fixed-dose combination therapy for glaucoma without a beta-blocker that is available in the United States.14

Commenting on the FDA approval of the new combination therapy, Gregory J. Katz, MD, Glaucoma Service, St Joseph Mercy Medical Center, Ann Arbor, MI, stated, “Glaucoma must be treated over the course of one’s life, and elevated eye pressure must be managed every day. It’s exciting to now have a product available that combines 2 effective compounds into one multidose combination, offering sustained control.”14

Dosing

Simbrinza contains the fixed dose combination of 10 mg/mL of brinzolamide plus 2 mg/mL of brimonidine tartrate.15 The recommended dosage of brinzolamide/brimonidine fixed-dose combination is 1 drop in the affected eye(s) 3 times daily. If more than 1 topical ophthalmic drug is being used, the drugs should be administered at least 5 minutes apart.15

Mechanism of Action

Simbrinza is a combination of 2 agents that decrease elevated IOP—brinzolamide, a carbonic anhydrase inhibitor, and brimonidine tartrate, an alpha-2 adrenergic receptor agonist.

Brinzolamide inhibits carbonic anhydrase in the ciliary processes of the eye to decrease aqueous humor secretion, presumably by slowing the formation of bicarbonate ions and with subsequent reduction in sodium and fluid transport.15 Brinzolamide has a peak ocular hypotensive effect occurring between 2 and 3 hours after dosing.15

Brimonidine tartrate has a peak ocular hypotensive effect that occurs 2 hours after dosing. The result is a reduction in IOP.15

Clinical Studies

The FDA approval of brinzolamide/brimonidine combination was based on 2 pivotal phase 3 clinical trials that involved approximately 1300 patients with open-angle glaucoma or with ocular hypertension.14 These studies, both 3 months in duration, assessed the IOP-lowering effect of brinzolamide 1%/brimonidine 0.2% ophthalmic suspension dosed 3 times daily compared with individually administered 1% brinzolamide 3 times daily and 0.2% brimonidine 3 times daily.16,17 The IOP-lowering effect of brinzolamide/brimonidine ophthalmic suspension was 1 mm Hg to 3 mm Hg greater than the effect of monotherapy with either 1% brinzolamide or with 0.2% brimonidine throughout the duration of the clinical trials.15,17 Table 1 shows the least square means for IOP (mm Hg) and the results of study 1 at week 2, week 6, and month 3.15 Table 2 shows the results for study 2.15

In both studies, the baseline mean IOP values were similar among treatment groups at all the 4 time points that were measured.16,17 Furthermore, the primary end points were achieved in both studies, and the brinzolamide/brimonidine combination was shown to be statistically superior at lowering IOP at month 3 for all time points compared with each of the individual components of the combination.16,17 In both studies, the brinzolamide/brimonidine combination therapy also achieved between a 5-mm Hg to 9-mm Hg reduction from baseline to month 3.14,16,17 In addition, the safety profile of the brinzolamide/brimonidine combination was similar to the safety profile of each of the individual components of the combination alone.16,17

Safety Profile

Adverse Events

The most common adverse reactions, occurring in approximately 3% to 5% of patients, included blurred vision, eye irritation, dysgeusia, dry mouth, and eye allergy.15 Brinzolamide is a sulfonamide, and although it is administered topically, it is absorbed systemically. Ad-
verse reactions attributed to sulfonamide may occur. Fatalities have occurred as a result of severe reactions to sulfonamides.15 Sensitization may recur when a sulfonamide is readministered, regardless of the route of administration. If signs of serious reactions or hypersensitivity occur, brinzolamide plus brimonidine should be discontinued.15

**Precautions**

The management of patients with acute angle-closure glaucoma requires therapeutic interventions in addition to ocular hypotensive agents. The combination of brinzolamide plus brimonidine has not been studied in patients with acute angle-closure glaucoma.

Brinzolamide/brimonidine is associated with an increased potential for developing corneal edema in patients with low endothelial cell counts.15 The preservative in brinzolamide/brimonidine—benzalkonium chloride—may be absorbed by soft contact lenses. Therefore, contact lenses should be removed during the administration of brinzolamide/brimonidine and may be reinserted 15 minutes after administration.15

Brimonidine tartrate, a component of the brinzolamide/brimonidine combination, had a <5% mean decrease in blood pressure 2 hours after dosing in clinical studies; caution should be exercised in treating patients with severe cardiovascular disease.15 In addition, brimonidine tartrate 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 thromboangiitisobliterans.15

There have been reports of bacterial keratitis associ-
ated 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.15

Brinzolamide/brimonidine ophthalmic suspension has not been specifically studied in patients with severe hepatic or renal impairment, and it is not recommended in these patients.15

**Contraindications**

Brinzolamide plus brimonidine is contraindicated in patients who are hypersensitive to any component of this medication, and in neonates and in infants (aged <2 years).15

**Drug Interactions**

The concomitant administration of brinzolamide/brimonidine ophthalmic suspension with oral carbonic anhydrase inhibitors is not recommended because of the potential additive effect of these medications. The use of brinzolamide/brimonidine with high-dose salicylate may result in acid-base and electrolyte alterations. Moreover, its use with central nervous system depressants may result in an additive or potentiating effect.15

The concomitant use of brinzolamide/brimonidine ophthalmic suspension with antihypertensives or with cardiac glycosides may result in an additive or potentiating effect on blood pressure lowering.15

The use of the brinzolamide/brimonidine combination with tricyclic antidepressants may blunt the hypotensive effect of systemic clonidine, and it is unknown whether its use with this class of drugs interferes with the effect of IOP lowering. The use of the ophthalmic suspension combination with monoamine oxidase inhibitors may result in increased hypotension.15

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**Table 2** Study 2: Brinzolamide/Brimonidine Combination Therapy versus Brinzolamide or Brimonidine Alone*

<table>
<thead>
<tr>
<th>Study 2 time points</th>
<th>Brinzolamide/brimonidine combination therapy (N = 218)</th>
<th>Brinzolamide (N = 229)</th>
<th>Brimonidine (N = 232)</th>
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<tbody>
<tr>
<td></td>
<td>Mean intraocular pressure, mm Hg</td>
<td>Mean intraocular pressure, mm Hg</td>
<td>Difference (95% CI)*</td>
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<tr>
<td><strong>Week 2</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>8:00 AM</td>
<td>20.5</td>
<td>22.2</td>
<td>-1.7 (-2.4 to -1.0)</td>
</tr>
<tr>
<td>10:00 AM</td>
<td>17.4</td>
<td>20.7</td>
<td>-3.3 (-4.0 to -2.6)</td>
</tr>
<tr>
<td>3:00 PM</td>
<td>18.7</td>
<td>20.5</td>
<td>-1.7 (-2.4 to -1.1)</td>
</tr>
<tr>
<td>5:00 PM</td>
<td>16.5</td>
<td>20.1</td>
<td>-3.6 (-4.3 to -2.9)</td>
</tr>
<tr>
<td><strong>Week 6</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8:00 AM</td>
<td>20.7</td>
<td>21.9</td>
<td>-1.2 (-1.9 to -0.5)</td>
</tr>
<tr>
<td>10:00 AM</td>
<td>17.4</td>
<td>20.5</td>
<td>-3.1 (-3.8 to -2.4)</td>
</tr>
<tr>
<td>3:00 PM</td>
<td>19.3</td>
<td>20.2</td>
<td>-0.8 (-1.5 to -0.2)</td>
</tr>
<tr>
<td>5:00 PM</td>
<td>16.9</td>
<td>19.9</td>
<td>-3.0 (-3.7 to -2.3)</td>
</tr>
<tr>
<td><strong>Month 3</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
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<td>21.1</td>
<td>22.0</td>
<td>-1.0 (-1.7 to -0.3)</td>
</tr>
<tr>
<td>10:00 AM</td>
<td>18.0</td>
<td>20.8</td>
<td>-2.8 (-3.5 to -2.1)</td>
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<td>3:00 PM</td>
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<td>5:00 PM</td>
<td>17.2</td>
<td>20.4</td>
<td>-3.2 (-3.9 to -2.5)</td>
</tr>
</tbody>
</table>

*Based on the intent-to-treat population, defined as all patients who received the study drug.

These estimates are based on least square means derived from a linear mixed model that accounts for correlated intraocular pressure measurements within patient; the difference reflects the results with brinzolamide/brimonidine combination therapy minus the individual component.

CI indicates confidence interval.

Source: Simbrinza (brinzolamide/brimonidine tartrate) ophthalmic suspension [prescribing information]. Fort Worth, TX: Alcon Laboratories, Inc; 2013.
Conclusion

A new treatment option for patients with open-angle glaucoma or with ocular hypertension became available in April 2013 when the FDA approved Simbrinza, the fixed-dose combination of 1% brinzolamide, a carbonic anhydrase inhibitor, and 0.2% brimonidine tartrate, an alpha-2 adrenergic receptor agonist. Brinzolamide/brimonidine ophthalmic suspension is the first combination therapy approved for glaucoma in the United States that does not contain a beta-blocker.

The approval of this new combination therapy was based on 2 pivotal clinical trials of approximately 1300 patients with open-angle glaucoma or with ocular hypertension. In both studies, the combination therapy was significantly superior to the individual components of the combination at lowering IOP in patients with open-angle glaucoma.

References

15. Simbrinza (brinzolamide/brimonidine tartrate) ophthalmic suspension [prescribing information]. Fort Worth, TX: Alcon Laboratories, Inc; 2013.