Therapeutic Class Overview
Ophthalmic Carbonic Anhydrase Inhibitors

Therapeutic Class Overview/Summary:
Glaucoma is an optic neuropathy that causes gradual degeneration of the cells making up the optic nerve. It is the leading cause of blindness and second leading cause of vision loss in the world.[1] Four distinct types of glaucoma include primary open-angle, acute angle-closure, secondary and congenital. Patients with open-angle glaucoma initially experience peripheral visual field loss, followed by central field loss, which may progress to irreversible blindness if untreated. The exact etiology of open-angle glaucoma is unknown. Major risk factors for developing open-angle glaucoma include advanced age, African or Hispanic/Latino descent, elevated intraocular pressure (IOP), family history of glaucoma or a central corneal thickness of less than 545 micrometers.[2-3] Other possible risk factors that have been investigated include low ocular systolic perfusion pressure, low systolic blood pressure, cardiovascular disease, hypertension, diabetes mellitus and hypothyroidism.[1,3-6]

IOP is the one major risk factor for glaucoma that is treatable. Available evidence suggests that lowering IOP inhibits or reduces the progression of optic nerve damage.[1-3,7] Treatment may be initiated in patients with a raised IOP despite having no visual field loss or optic nerve damage. An IOP greater than 22 mm Hg is generally considered to be elevated and would be treated by most clinicians; however, this number varies according to screening methods, risk factors and disease progression.[7] The target IOP should be individualized based on their response to therapy and disease progression. There is no consensus target IOP below which further visual loss and optic nerve damage will be prevented.[2,3]

This class review consists of the ophthalmic carbonic anhydrase inhibitors, which includes brinzolamide (Azopt®), dorzolamide hydrochloride (Trusopt®), and the fixed dose combination products brinzolamide/brimonidine tartrate and dorzolamide hydrochloride/timolol maleate (Cosopt®).[9-13] Brinzolamide, dorzolamide and brinzolamide/brimonidine are Food and Drug Administration (FDA) approved for the treatment of elevated IOP in patients with ocular hypertension or open-angle glaucoma, while dorzolamide/timolol is indicated for the treatment of elevated IOP in patients with ocular hypertension or open-angle glaucoma who had insufficiently responded to beta blockers .[9-13]

Table 1. Current Medications Available in the Therapeutic Class[9-13]

Generic (Trade Name)	Food and Drug Administration-Approved Indications	Dosage Form/Strength	Generic Availability
Single Entity Agents			
Brinzolamide (Azopt®)	Treatment of Elevated Intraocular Pressure Due to Ocular Hypertension or Open-Angle Glaucoma	Ophthalmic suspension: 1%	-
Dorzolamide (Trusopt®*)	Treatment of Elevated Intraocular Pressure Due to Ocular Hypertension or Open-Angle Glaucoma	Ophthalmic solution: 2%	✔
Combination Products			
Brinzolamide/brimonidine (Simbrinza®)	Treatment of Elevated Intraocular Pressure Due to Ocular Hypertension or Open-Angle Glaucoma	Ophthalmic suspension: 1%/0.2%	-
Dorzolamide/timolol (Cosopt®*, Cosopt PF®)	Treatment of Elevated Intraocular Pressure Due to Ocular Hypertension or Open-Angle Glaucoma†	Ophthalmic solution: 22.3-6.8 mg/mL	✔

*Generic available in at least one dosage form or strength.

†Indicated for the reduction of intraocular pressure in patients with open-angle glaucoma or ocular hypertension who are insufficiently responsive to beta-blockers (failed to achieve target intraocular pressure after multiple measurements over time).

Evidence-based Medicine

- Single agent ophthalmic carbonic anhydrase inhibitors, brinzolamide and dorzolamide, were evaluated in a prospective, multicenter, parallel group study. Reduction in IOP from baseline was statistically significant in each group (P<0.001); though, the changes in IOP from baseline were comparable between the treatment groups (P value not reported).[16] Similar reductions in IOP were also observed when the agents were used in combination with ophthalmic timolol.[18]
- Ophthalmic brimonidine was associated with a significantly greater reduction in IOP than either ophthalmic brinzolamide or ophthalmic dorzolamide (all in combination with a prostaglandin) after one and four months of therapy (P<0.001 for both groups).[20]
- The FDA-approval of brinzolamide/brimonidine was based on two randomized, double-blind, active-controlled clinical trials. Each trial patients with open-angle glaucoma or ocular hypertension for three months. Brinzolamide/brimonidine 1%/0.2% was administered three times daily and compared to individually administered 1% brinzolamide three times daily and 0.2% brimonidine tartrate three times daily. In the first study, the mean IOP of the brinzolamide/brimonidine treatment group was significantly lower than that of the brinzolamide or brimonidine groups (P<0.002, for all comparisons). Study two also found a statistically significant difference in IOP in favor of brinzolamide/brimonidine when compared to each individual component (P≤0.005 for all comparisons).[13,21,22]
- The efficacy of ophthalmic dorzolamide/timolol was compared against its individual components as well as agents in other ophthalmic classes. Ophthalmic dorzolamide/timolol demonstrated a greater decrease in IOP compared to monotherapy with ophthalmic dorzolamide or ophthalmic timolol (*P* value not reported).[31,32]
- When ophthalmic dorzolamide/timolol was compared to ophthalmic brimonidine/timolol, both therapies were associated with significant reductions in IOP from baseline and the difference between groups was not found to be significant (P value not reported).[24-28]
- Two large meta-analyses evaluated the relative efficacy of ophthalmic formulations of prostaglandin analogues, beta blockers, alpha agonists, and carbonic anhydrous inhibitors in reducing IOP.[45,47] These trials concluded that the largest reduction in IOP occurred with ophthalmic prostaglandin analogues and ophthalmic timolol maleate. Ophthalmic carbonic anhydrase inhibitors were associated with a lower relative reduction in IOP; though, the changes from baseline were statistically significant among patients receiving ophthalmic carbonic anhydrase inhibitors.

Key Points within the Medication Class

- According to Current Clinical Guidelines:
    - Current guidelines by the American Academy of Ophthalmology and American Optometric Association recommend ophthalmic β adrenergic antagonists and prostaglandin analogues as first-line pharmacologic therapy in patients with elevated IOP.[2]
    - Combination or monotherapy with agents from an alternative pharmacologic class is recommended for patients that experience intolerable adverse events or who do not achieve the optimal IOP reduction with first-line agents.[2]
- Other Key Facts:
    - Currently ophthalmic dorzolamide (Trusopt®) and dorzolamide/timolol (Cosopt®) are available generically.
    - Brinzolamide (Azopt®), brinzolamide/brimonidine (Simbrinza®) and dorzolamide/timolol preservative-free (Cosopt-PF®) are available as brand name products only.

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