

Ophthalmics, Glaucoma Agents Review

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Ophthalmics, Glaucoma Agents Review

FDA-Approved Indications¹

Drug	Manufacturer	Reduction of elevated IOP in ocular hypertension	Reduction of elevated IOP in open-angle glaucoma
Miotics, Topical			
pilocarpine ²	generic		X
Sympathomimetics			
apraclonidine (Iopidine [®]) ³	Alcon	X*	X*
brimonidine (Alphagan P [®] , generics) ^{4,5}	Allergan, generic	X	X
dipivefrin (Propine [®])	Allergan		X
Beta-blockers			
betaxolol (Betoptic S [®] , generics) ⁶	Alcon, generic	X	X
carteolol (Ocupress [®])	generic	X	X
levobunolol (Betagan [®])	generic	X	X
metipranolol (Optipranolol [®])	generic	X	X
timolol (Betimol [®] , generics) ^{7,8}	Vistakon, generic	X	X
timolol LA (Istalol [®]) ⁹	Ista	X	X
Carbonic Anhydrase Inhibitors			
brinzolamide (Azopt [®]) ¹⁰	Alcon	X	X
dorzolamide (Trusopt [®]) ¹¹	generic	X	X
Combination Products			
brimonidine/timolol (Combigan [™]) ¹²	Allergan	X**	X**
dorzolamide/timolol (Cosopt [®]) ¹³	generic	X***	X***
Prostaglandin Analogs			
bimatoprost (Lumigan) ¹⁴	Allergan	X	X
latanoprost (Xalatan [®]) ¹⁵	Pfizer	X	X
travoprost (Travatan [®] , Travatan [®] Z) ^{16,17}	Alcon	X***	X***

IOP = intraocular pressure

* indicated as short-term adjunctive therapy in patients on maximally tolerated therapies

** indicated as adjunctive or replacement therapy

*** indicated as second-line therapy

Unlike Lumigan and Xalatan, Travatan and Travatan Z are indicated for the reduction of intraocular pressure in patients with open-angle glaucoma or ocular hypertension only if they are intolerant of other intraocular lowering medications or insufficiently responsive to another intraocular pressure lowering agent.

Apraclonidine (Iopidine) 0.5% is indicated for short-term adjunctive therapy in patients on maximally tolerated medical therapy who require additional intraocular pressure (IOP) reduction. Patients on maximally tolerated medical therapy who are treated with apraclonidine to delay surgery should have frequent follow-up examinations and treatment should be discontinued if the intraocular pressure rises significantly.

Apraclonidine 1% is indicated to control or prevent post-surgical elevations in IOP that occur in patients after argon laser trabeculoplasty, argon laser iridotomy, or Nd:YAG posterior capsulotomy.¹⁸

Overview

Glaucoma is the second most common cause of permanent blindness in the United States and the most common cause of blindness among African-Americans. The prevalence of glaucoma in the United States in adults over 40 years old is estimated at 1.86 percent.¹⁹ As the American population ages, prevalence is expected to rise.²⁰ African-Americans have a higher prevalence compared to Caucasians; however, Caucasians have a steeper rise in open-angle glaucoma associated with advancing age.^{21,22} Generally, glaucoma occurs more frequently in men.²³

Increased intraocular pressure (IOP) is common in glaucoma and is believed to contribute to the damage to the optic nerve, which can lead to loss of visual sensitivity and field. IOP is no longer considered a diagnostic criterion for glaucoma. Two major types of glaucoma have been identified: open-angle and closed-angle. In open-angle glaucoma, there is reduced flow through the trabecular meshwork. Open-angle glaucoma accounts for the majority of cases. In closed-angle glaucoma, the iris is pushed forward against the trabecular meshwork, blocking fluid from escaping. Ocular hypertension may precede glaucoma in some patients. Some of the risk factors for the development of glaucoma include elevated IOP, advancing age, family history of glaucoma, African-American or Hispanic descent, and decreased central corneal thickness.^{24,25,26,27,28}

Reduction of IOP may be achieved either by decreasing the rate of production of aqueous humor or increasing the rate of outflow of aqueous humor from the anterior chamber of the eye.²⁹ Topical ocular hypotensive agents can delay or prevent the development of primary open-angle glaucoma in some patients.³⁰ In African-Americans with ocular hypertension, the use of topical ocular hypotensive agents has been shown to delay or prevent the onset of primary open-angle glaucoma.³¹

All medications used for the management of glaucoma attempt to limit further damage to the optic nerve. Medication classes used in the management of glaucoma include beta-blockers, miotics, sympathomimetics, topical carbonic anhydrase inhibitors, and prostaglandin analogs. Monotherapy or combination therapy may be used to treat glaucoma and delay the need for surgery and prevent functional vision loss. According to the American Academy of Ophthalmology, prostaglandin analogs and beta blockers are the most frequently used eye drops, but no further guidance is provided.³²

Pharmacology³³

Drug	Decreased aqueous humor production	Increased trabecular outflow	Increased uveoscleral outflow
Miotics, Topical			
pilocarpine		X	
Sympathomimetics			
apraclonidine (Iopidine)	X	X	X
brimonidine (Alphagan P)	X		X
dipivefrin (Propine)		X	X
Beta-blockers			
betaxolol (Betoptic S)	X		
carteolol (Ocupress)	X		
levobunolol (Betagan)	X		
metipranolol (Optipranolol)	X		
timolol (Betimol, Timoptic, Timoptic XE, Istalol)	X		
Carbonic Anhydrase Inhibitors			
brinzolamide (Azopt)	X		
dorzolamide (Trusopt)	X		
Combination Products			
brimonidine/timolol (Combigan)	X		X
dorzolamide/timolol (Cosopt)	X		
Prostaglandin Analogs			
bimatoprost (Lumigan)		X	X
latanoprost (Xalatan)			X
travoprost (Travatan, Travatan Z)		X	X

Pharmacokinetics

Systemic absorption occurs with topical beta-blockers, topical ophthalmic sympathomimetics, topical carbonic anhydrase inhibitors, and topical direct-acting miotics including pilocarpine.^{34,35,36,37,38,39,40,41} Potential for systemic adverse effects exists for these classes.

Below is a summary of the pharmacokinetics for the prostaglandin analogs.

Drug	Pro-drug	Metabolism	Excretion (%)	Onset (hours)	Maximum effect (hours)
bimatoprost (Lumigan) ⁴²	No	Liver – many metabolites	Urine: 67 Feces: 25	4	8-12
latanoprost (Xalatan) ⁴³	Yes - hydrolyzed by esterases to active free acid	Liver – two metabolites	Urine: 88	3-4	8-12
travoprost (Travatan, Travatan Z) ^{44,45}	Yes – hydrolyzed by esterases to active free acid	Liver – inactive metabolites	Rapid systemic elimination	2	After 12

Travatan contains travoprost 0.004% and has benzalkonium chloride (BAC) 0.015% as the preservative. Travatan Z contains travoprost 0.004% with a different preservative, sofZia™. SofZia contains boric acid, propylene glycol, sorbitol, and zinc chloride, and is reportedly less irritating than benzalkonium chloride.⁴⁶

Brimonidine (Alphagan P) 0.1% and 0.15% ophthalmic solutions contain Purite 0.005% as the preservative. Brimonidine 0.2% (Alphagan), using BAC, has been associated with a higher incidence of allergic reactions in clinical trials.^{47,48}

Timolol ophthalmic gel-forming solution (Timoptic XE) contains benzododecinium bromide as the preservative.

All other products in this class contain benzalkonium chloride as a preservative.

Contraindications/Warnings

Patients prescribed IOP-lowering medication should be routinely monitored for IOP changes. As with all multidose ophthalmic products, contamination of the bottle contents may result in infections including bacterial keratitis.

Contraindications

Dorzolamide/timolol (Cosopt) and brimonidine/timolol (Combigan) are contraindicated in patients with bronchial asthma, a history of bronchial asthma, severe chronic obstructive pulmonary disease (COPD), sinus bradycardia, second or third degree atrioventricular block, overt cardiac failure, cardiogenic shock, or hypersensitivity to any component of the product.^{49,50}

Beta-blockers are generally contraindicated in patients with sinus bradycardia, second or third degree atrioventricular block, cardiogenic shock, or patients with overt cardiac failure.^{51,52,53,54,55}

Apraclonidine (Iopidine) and brimonidine (Alphagan / P) are contraindicated in patients receiving monoamine oxidase (MAO) inhibitors.^{56,57}

The addition of apraclonidine 0.5% as part of a patient's maximally tolerated medical therapy may not provide additional benefit if two aqueous humor-suppressing drugs, such as beta-blockers and carbonic anhydrase inhibitors, are already being used.^{58,59} Apraclonidine is an aqueous humor-suppressing drug and the addition of a third drug of similar action may not significantly reduce IOP. The IOP-lowering efficacy of apraclonidine diminishes over time in some patients; the benefit for most patients is less than one month.

Brinzolamide (Azopt) and dorzolamide (Trusopt) are sulfonamides administered topically but absorbed systemically. Adverse effects attributable to sulfonamides are also possible with brinzolamide; these adverse effects include rare fatalities, 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 by any route. If signs of hypersensitivity develop, discontinue the medication.

Warnings

Beta-blockers^{60,61,62,63,64,65,66}

Topically applied ophthalmic beta-blockers are systemically absorbed and may produce systemic adverse effects. Reported adverse effects include death due to bronchospasm in patients with asthma and cardiac failure. Beta-blockers can depress myocardial contractility and result in heart failure in patients with and without a history of cardiac failure.

Caution should be used when prescribing beta-blocker therapy in patients with COPD of mild or moderate severity, bronchospastic disease, or a history of bronchospastic disease. Using agents other than beta-blockers may be more appropriate for patients with these concurrent disease states. Sympathetic stimulation may be essential for support of the circulation in individuals with diminished myocardial contractility, and its inhibition by beta-adrenergic receptor blockade may precipitate more severe heart failure.

In patients without a history of cardiac failure, continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of cardiac failure, ophthalmic beta-blocker therapy should be discontinued.

Caution should also be used with beta-blockers in patients with diabetes mellitus as beta-blockers can mask the signs and symptoms of acute hypoglycemia. Beta-blockers may mask certain clinical signs such as tachycardia of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta-blockers that might precipitate a thyroid storm.

Prostaglandin analogs^{67,68,69}

All prostaglandin analogs can cause permanent changes to ocular tissues by increasing pigmentation of the iris and eyelid and growth of eyelashes. Gradual change in eye color to brown may occur due to the increased number of melanosomes in melanocytes. Therapy may need to be discontinued if the increased pigmentation continues. Once discontinued, the pigmentation will not continue to increase, but the resultant color change may be permanent. The long-term effects of this pigmentation change are not known.

Latanoprost 0.005% (Xalatan) once daily has been evaluated for five years for safety and efficacy in patients with primary open-angle or exfoliation glaucoma.⁷⁰ Enrolled patients initially participated in a three-year, open-label, prospective trial and then entered a two-year extension phase. A total of 519 patients started the study with 380 patients participating in the two-year extension phase. After five years, iris pigmentation was observed in a small number of patients. For patients with iris pigmentation changes, the onset occurred within the first 24 months in 94 percent of patients. The rate of progression of pigmentation change decreased over time. The mean IOP was reduced by 25 percent from baseline throughout the observation period of five years with 70 percent of patients not requiring a change in therapy.

With bimatoprost (Lumigan), onset of iris pigmentation occurs in the first year of therapy for the majority of patients.⁷¹ For those who do have iris pigmentation associated with bimatoprost, increasing iris pigmentation has been observed for up to five years. The iris pigmentation did not affect the incidence or severity of other adverse effects. The effects of increased pigmentation beyond five years are not known.

All agents may gradually change eyelashes by increasing length, thickness, pigmentation, and number of lashes. These changes are especially important when medication is administered to one eye only.

Sympathomimetics^{72,73,74,75}

Although brimonidine had minimal effect on the blood pressure of patients in clinical studies, caution should be exercised in treating patients with severe cardiovascular disease. Brimonidine has not been studied in patients with hepatic or renal impairment; caution should be used in treating such patients. Brimonidine should be used with caution in patients with depression, cerebral or coronary insufficiency, Raynaud's phenomenon, orthostatic hypotension, or thromboangiitis obliterans. No evidence of cross-reactive allergic responses to brimonidine in patients with known allergy to apraclonidine has been found.⁷⁶

Use of apraclonidine ophthalmic solution can lead to an allergic-like reaction characterized wholly or in part by the symptoms of hyperemia, pruritus, discomfort, tearing, foreign body sensation, and edema of the lids and conjunctiva. Discontinue apraclonidine ophthalmic solution therapy if ocular allergic-like symptoms occur.

Apraclonidine and brimonidine can cause fatigue, dizziness and/or drowsiness. Warn patients who engage in hazardous activities requiring mental alertness of the potential for a decrease in mental alertness while using these agents.

Others

Pilocarpine is contraindicated in patients with a history of retinal detachment, acute iritis, or other conditions which pupillary constriction is contraindicated.⁷⁷

Drug Interactions

Beta-blockers^{78,79,80,81,82,83,84}

Ophthalmic beta-blockers given with oral therapy such as calcium channel blockers, beta blockers, or digitalis may have additive effects in prolonging the atrioventricular conduction time. In patients with impaired cardiac function, use of ophthalmic beta blockers with calcium channel blockers should be avoided.

The use of two beta-blockers for ophthalmic purposes is not recommended.

Potentiated systemic beta-blockade (e.g., decreased heart rate, depression) has been reported during combined treatment with CYP2D6 inhibitors (e.g., quinidine, SSRIs) and timolol (Timoptic).

Carbonic anhydrase inhibitors^{85,86}

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 dorzolamide (Trusopt) or dorzolamide with timolol (Cosopt). Concurrent use is not recommended.

Prostaglandin Analogs⁸⁷

Ophthalmic products containing thimerosal should be administered at least five minutes apart from latanoprost (Xalatan) as precipitation has been reported.

Sympathomimetics^{88,89,90,91}

Specific drug interaction studies have not been performed with brimonidine (Alphagan, P) and apraclonidine (Iopidine). The possibility exists with brimonidine and apraclonidine that an additive or potentiating effect with CNS depressants (alcohol, barbiturates, opiates, sedatives, or anesthetics) should be considered. Alpha-agonists, as a class, may reduce pulse and blood pressure. Caution in using concomitant drugs such as antihypertensives and/or cardiac glycosides is advised.

Use caution with coadministration of agents in this class with tricyclic antidepressants (TCAs), as case reports of TCAs blunting the hypotensive effect of systemic clonidine exist. It is not known whether the concurrent use of these agents with apraclonidine can lead to a reduction in IOP-lowering effect. Caution, however, is advised in patients taking TCAs which can affect the metabolism and uptake of circulating amines. Apraclonidine should not be used in patients receiving MAO inhibitors.

Adverse Effects

Drug	Blepharitis	Conjunctival hyperemia	Conjunctivitis (all types)	Ocular dryness	Burning and/or stinging	Foreign body sensation	Itching	Ocular pain	Photophobia	Tearing	Visual acuity change, visual disturbance	Other
Miotics, Topical												
pilocarpine ⁹²	nr	nr	nr	nr	nr	nr	nr	*	nr	*	*	
Sympathomimetics												
apraclonidine 0.5% (Iopidine) ⁹³	<1	5-15	1-5	1-5	*	1-5	5-15	<1	<1	1-5	1-5	10 percent: oral dryness
apraclonidine 1% (Iopidine) ⁹⁴	nr	nr	nr	*	*	*	*	nr	nr	nr	*	
brimonidine 0.15% (Alphagan P) ⁹⁵	1-4	10-20	10-20	1-4	*	1-4	10-20	1-4	1-4	1-4	5-9	5-9 percent: oral dryness
brimonidine 0.2% (Alphagan) ⁹⁶	3-9	3-30	10-30	3-9	10-30	10-30	10-30	3-9	3-9	3-9	10-30	10-30 percent: oral dryness
dipivefrin (Propine) ⁹⁷	*	6	*	nr	6	nr	*	*	2	nr	*	
Beta-blockers												
betaxolol (Betoptic S) ⁹⁸	nr	*	nr	*	*	*	*	*	*	*	*	
carteolol (Ocupress) ⁹⁹	*	25	*	nr	25	nr	nr	nr	*	25	*	
levobunolol (Betagan) ¹⁰⁰	nr	nr	nr	nr	30	nr	nr	nr	nr	nr	nr	
metipranolol (Optipranolol) ¹⁰¹	*	*	*	nr	*	nr	nr	nr	*	*	*	
timolol (Timoptic) ¹⁰²	*	nr	*	*	12.5	*	*	*	nr	*	*	
timolol gel forming solution (Timoptic XE) ¹⁰³	*	nr	1-5	*	nr	1-5	1-5	1-5	nr	1-5	30	
timolol LA (Istalol) ¹⁰⁴	*	*	nr	*	38	*	4-10	*	nr	*	4-10	

Adverse effects are reported as a percentage. Adverse effects data are obtained from package information and should not be considered comparative.
 *= Reported. nr = not reported

Adverse Effects (continued)

Drug	Blepharitis	Conjunctival hyperemia	Conjunctivitis (all types)	Ocular dryness	Burning and/or stinging	Foreign body sensation	Itching	Ocular pain	Photophobia	Tearing	Visual acuity change, visual disturbance	Other
Carbonic Anhydrase Inhibitors												
brinzolamide (Azopt) ¹⁰⁵	1-5	nr	< 1	1-5	nr	1-5	1-5	1-5	nr	<1	5-10	5-10 percent: bitter taste
dorzolamide (Trusopt) ^{106,107}	nr	1-5	nr	1-5	nr	nr	nr	*	1-5	1-5	1-5	25 percent: bitter taste
Combination Products												
brimonidine/timolol (Combigan) ¹⁰⁸	1-5	5-15	5-15	1-5	5-15	1-5	5-15	5-15	<1	<1	1-5	5-15 percent: conjunctival folliculosis
dorzolamide/timolol (Cosopt) ¹⁰⁹	1-5	5-15	1-5	1-5	*	1-5	5-15	1-5	<1	1-5	5-15	< 30 percent: taste perversion
Prostaglandin Analogs												
bimatoprost (Lumigan) ¹¹⁰	3-10	15-45	1-3	3-10	3-10	3-10	15-45	3-10	1-3	1-3	3-10	15-45 percent eyelash growth
latanoprost (Xalatan) ¹¹¹	nr	5-15	<1	1-4	nr	5-15	5-15	1-4	1-4	1-4	5-15	eyelash growth
travoprost (Travatan) ¹¹²	1-4	35-50	1-4	1-4	nr	5-10	5-10	5-10	1-4	1-4	5-10	eyelash growth
travoprost (Travatan Z) ¹¹³	1-4	30-50	1-4	1-4	nr	5-10	5-10	5-10	1-4	1-4	5-10	eyelash growth

Adverse effects are reported as a percentage. Adverse effects data are obtained from package information and should not be considered comparative.

*= Reported. nr = not reported

In two clinical studies in patients with elevated IOP, brinzolamide (Azopt) was associated with less stinging and burning upon instillation than dorzolamide (Trusopt).^{114,115}

One report suggests that betaxolol administered as the suspension (Betoptic S) reduces the incidence of stinging upon instillation.¹¹⁶

Systemic reactions to ophthalmic administration of beta-blockers include the following: exacerbation of asthma and COPD, heart failure, arrhythmias including bradycardia, heart block, hypotension, masking signs of hypoglycemia, CNS reactions including depression, and sexual dysfunction.^{117,118,119,120}

Special Populations

Pediatrics^{121,122,123,124,125,126,127,128,129}

Brimonidine 0.2% (Alphagan), brimonidine/timolol (Combigan), and dorzolamide/timolol (Cosopt) have been studied in well controlled clinical trials involving children ages two years and older.^{130,131,132} Somnolence is the most common adverse effect with brimonidine use and is seen in up to 50 to 83 percent of children ages two to six years. Decreased alertness has also been reported with brimonidine. In children ages seven years and older, patients reported somnolence (25 percent) with brimonidine. The safety and effectiveness of brimonidine ophthalmic solution have not been studied in pediatric patients below the age of two years. In study with 32 children, mean age 10.5 years, brimonidine significantly reduced IOP (mean decrease of 6.7 percent; $p=0.04$).¹³³ Data on reduction in IOP was only available for 11 of 32 children enrolled in the study. Two young children (ages 2.4 and 3.7 years) repeatedly were unarousable soon after the administration of brimonidine. Five other children experienced extreme fatigue after brimonidine administration. All symptoms resolved after brimonidine was discontinued. The study concluded that brimonidine should be used with caution in young children because of the potential for CNS depression.

Dorzolamide (Trusopt) has been studied in a well-controlled pediatric clinical trial of three months duration.^{134,135} Safety and effectiveness of dorzolamide and timolol (Timoptic) have been established when administered individually in pediatric patients aged two years and older. Use of these drug products in these children is supported by evidence from adequate and well-controlled studies in children and adults. Safety and efficacy in pediatric patients below the age of two years have not been established for these two agents.

Safety and effectiveness of brimonidine/timolol (Combigan) have been established for ages two to 16 years. Use of brimonidine/timolol in pediatric patients is supported by evidence from adequate and well-controlled studies of brimonidine/timolol in adults with additional data from a study of the concomitant use of brimonidine ophthalmic solution 0.2% and timolol maleate ophthalmic solution in pediatric glaucoma patients (ages two to seven years). Brimonidine/timolol is not recommended for use in children under the age of two years.¹³⁶

Safety and IOP-lowering effect of betaxolol (Betoptic S) have been demonstrated in pediatric patients in a three-month, multicenter, double-masked, active-controlled trial.¹³⁷

For the other products, safety and effectiveness in pediatrics have not been established at this time.

Pregnancy^{138,139,140,141,142,143,144,145,146,147,148,149,150,151}

Most of the agents used in the treatment of ocular hypertension and glaucoma are Pregnancy Category C. Brimonidine (Alphagan P) and dipivefrin (Propine) are the exceptions, with Pregnancy Category B classifications.

African-Americans

Travoprost (Travatan) has been shown to provide additional IOP reduction in the African-American population compared to other populations.^{152,153}

Severe Renal or Hepatic Impairment^{154,155}

Although the topical use of apraclonidine ophthalmic solution has not been studied in renal failure patients, structurally related clonidine undergoes a significant increase in half-life in patients with severe renal impairment. Close monitoring of cardiovascular parameters in patients with impaired renal function is advised if they are candidates for topical apraclonidine therapy. Close monitoring of cardiovascular parameters in patients with impaired liver function is also advised as the systemic dosage form of clonidine is partially metabolized in the liver.

Brimonidine (Alphagan P) has not been well studied in patients with severe renal or hepatic impairment. Caution should be used in treating such patients.

Dosages¹⁵⁶

Drug	Strength	Dosing	Availability
Miotics, Topical			
pilocarpine	0.5, 1, 2, 3, 4, 6%	One drop up to four times daily	2 mL (1, 2, 4% only), 15 mL
Sympathomimetics			
apraclonidine (Iopidine) ¹⁵⁷	0.5%	One to two drops three times daily	5, 10 mL
apraclonidine (Iopidine) ¹⁵⁸	1%	One drop one hour prior to laser surgery; one drop immediately following a laser surgical procedure	1 mL unit dose
brimonidine (Alphagan P) ¹⁵⁹	0.1% and 0.15%	One drop three times daily	5, 10, 15 mL
brimonidine (Alphagan) ¹⁶⁰	0.2%	One drop three times daily	5, 10, 15 mL
dipivefrin (Propine)	0.1%	One drop twice daily	5, 10, 15 mL

Dosages (continued)¹⁶¹

Drug	Strength	Dosing	Availability
Beta-blockers			
betaxolol (Betoptic) ¹⁶²	0.5%	One to two drops twice daily	5, 10, 15 mL
betaxolol (Betoptic S)	0.25%	One to two drops twice daily	5, 10, 15 mL
carteolol (Ocupress)	1%	One drop twice daily	5, 10, 15 mL
levobunolol (Betagan)	0.25% and 0.5%	One to two drops once or twice daily	0.25% - 5, 10 mL 0.5% - 5, 10, 15 mL
metipranolol (Optipranolol)	0.3%	One drop twice daily	5, 10 mL
timolol solution (Betimol, Timoptic) ¹⁶³	0.25% and 0.5%	One drop twice daily	5, 10, 15 mL
timolol gel forming solution (Timoptic XE) ¹⁶⁴	0.25% and 0.5%	One drop daily	0.25% - 5 mL 0.5% - 2.5, 5 mL
timolol LA solution (Istalol) ¹⁶⁵	0.5%	One drop daily	2.5, 5 mL
Carbonic Anhydrase Inhibitors			
brinzolamide (Azopt) ¹⁶⁶	1%	One drop three times daily	5, 10, 15 mL
dorzolamide (Trusopt) ¹⁶⁷	2%	One drop three times daily	5, 10 mL
Combination Products			
brimonidine/timolol (Combigan) ¹⁶⁸	0.2% brimonidine and 0.5% timolol	One drop twice daily	5, 10 mL
dorzolamide/timolol (Cosopt) ¹⁶⁹	2% dorzolamide and 0.5% timolol	One drop twice daily	5, 10 mL
Prostaglandin Analogs			
bimatoprost (Lumigan) ¹⁷⁰	0.03%	One drop daily in evening	2.5, 5, 7.5 mL
latanoprost (Xalatan) ¹⁷¹	0.005%	One drop daily in evening	2.5 mL 2.5 mL x 3 packages
travoprost (Travatan, Travatan Z) ^{172,173}	0.004%	One drop daily in evening	2.5, 5 mL

When administering other ophthalmic drugs, a period of at least five minutes should elapse before administering one of the prostaglandin analogs.

Clinical TrialsSearch Strategy

Articles were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the use of all drugs in this class. Randomized, controlled, comparative trials are considered the most relevant in this category. Studies included for analysis in the review were published in English, performed with human participants and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question, and include follow-up (endpoint

assessment) of at least 80 percent of participants entering the investigation. Despite some inherent bias found in all studies including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship/funding must be considered, the studies in this review have also been evaluated for validity and importance. Studies administering only a single drop of medication were excluded. Studies evaluating combinations of two medications for the treatment of glaucoma not commercially available as a combination product in the United States have not been included in this review.

bimatoprost (Lumigan) and latanoprost (Xalatan)

In a study of 64 patients with open-angle glaucoma or ocular hypertension, bimatoprost 0.03%, latanoprost 0.005%, or vehicle given once daily in the evening were compared for safety and efficacy in a 30-day double-blind, randomized trial.¹⁷⁴ Baseline IOPs were 22 – 24 mm Hg in all the groups. Both agents significantly lowered IOP from baseline at days 14 and 29. At day 29, bimatoprost (-5.9 to -8 mm Hg) lowered IOP more than latanoprost (-4.4 to -7.6 mm Hg), but the difference was not statistically significant. Both agents had similar adverse events and were well tolerated.

A total of sixty patients with normal-tension glaucoma were enrolled in a multicenter, randomized, double-blind clinical trial to compare the IOP-lowering efficacy and safety of bimatoprost 0.03% and latanoprost 0.005%.¹⁷⁵ Patients underwent a washout period and then were randomized to daily bimatoprost 0.03% or latanoprost 0.005% for three months. Both active therapies had significant reductions in IOP compared to baseline at all diurnal measurements ($p < 0.001$). The morning (8 a.m.) measurement was significantly lower with bimatoprost at two follow-up visits ($p \leq 0.033$). After three months, the mean IOP reductions from baseline were -2.8 to -3.8 mm Hg (17.5 to 21.6 percent) with bimatoprost and -2.1 to -2.6 mm Hg (12.7 to 16.2 percent) for latanoprost. The overall mean reduction in IOP was greater with bimatoprost (-3.4 mm Hg, 19.9 percent) than latanoprost (-2.3 mm Hg, 14.6 percent; $p = 0.035$). Adverse effects and clinical success did not differ between the two groups.

bimatoprost (Lumigan) and travoprost (Travatan)

Due to a lack of double-blind trials comparing bimatoprost and travoprost, investigator-blinded trials have been included. In a multicenter, randomized, investigator-blinded trial, bimatoprost 0.03% was compared to travoprost 0.004% in 94 black patients with open-angle glaucoma or ocular hypertension over three months.¹⁷⁶ Each therapy was given once daily for three months. Both therapies significantly lowered IOP at all study visits ($p < 0.001$). Mean IOP reductions from baseline were -6.8 to -7.8 mm Hg (27 to 31 percent) for bimatoprost and -6.2 to -6.9 mm Hg (25 to 28 percent) for travoprost. By the end of the study, 85 and 68 percent of patients receiving bimatoprost and travoprost, respectively, achieved at least a 20 percent mean reduction of IOP. Patients with mean IOP reductions of at least 40 percent were reported in 31.9 and 20.9 percent for the bimatoprost and travoprost groups, respectively. Ocular redness was the most commonly reported adverse drug reaction in both groups.

In a randomized, investigator-blinded, parallel-group trial, 157 patients with glaucoma or ocular hypertension were enrolled to compare the IOP-lowering effects of bimatoprost 0.03% and travoprost 0.004% over six months.¹⁷⁷ Five study visits recorded IOP at three time points (9 a.m., 1 p.m., and 4 p.m.) and found no significant differences between the two treatment groups. Both drugs significantly lowered IOP at all time points ($p \leq 0.001$). The only time point with a significant difference between the therapies was at 9 a.m., when mean IOP reduction was

7.1 mm Hg (27.9 percent) for bimatoprost and 5.7 mm Hg (23.3 percent) with travoprost ($p=0.014$). Ocular redness was the most common adverse effect.

bimatoprost (Lumigan) and timolol (Timoptic)

In two identical, multicenter, randomized, double-masked, clinical trials, 1,198 patients were treated with bimatoprost 0.03% once or twice daily or timolol maleate 0.5%.¹⁷⁸ Bimatoprost once daily provided significantly lower mean IOP than timolol at 8 a.m., 10 a.m., and 4 p.m. at each study visit ($p<0.001$). This was also true for bimatoprost twice daily at most time points, but efficacy was inferior to the once daily regimen. At 10 a.m. during month 12, the mean reduction in IOP from baseline was 30 percent with bimatoprost and 21 percent with timolol ($p<0.001$). A significantly higher percentage of patients receiving bimatoprost daily (58 percent) than timolol (37 percent) achieved IOP at or below 17 mm Hg ($p<0.001$). The most common adverse effect with bimatoprost was hyperemia.

In a multicenter, randomized, double-masked trial, 596 patients diagnosed with ocular hypertension or glaucoma received bimatoprost 0.03% once or twice daily or timolol 0.5% twice daily.¹⁷⁹ Scheduled visits were conducted prestudy, baseline, weeks two and six, and month three. At month three, the mean reduction in IOP from baseline was 35.2 percent with bimatoprost once daily, 30.4 percent with bimatoprost twice daily, and 26.2 percent with timolol twice daily. At all follow-up visits, mean IOP reductions were significantly greater in the bimatoprost once daily group than in the timolol group at each time point ($p<0.001$). Twice-daily dosing of bimatoprost also provided significantly greater mean reductions in IOP than timolol at most time points, but it was not as effective as once daily dosing. Bimatoprost was associated with significantly more hyperemia and eyelash growth than timolol, whereas timolol was associated with significantly more burning and stinging sensation in the eyes.

bimatoprost (Lumigan) and dorzolamide/timolol (Cosopt)

In a multicenter, double-blind study, 177 patients with glaucoma or ocular hypertension who were not controlled after at least two weeks of timolol maleate 0.5% were randomized to bimatoprost 0.03% once daily or combined dorzolamide 2%/timolol 0.5% twice daily for three months.¹⁸⁰ Bimatoprost provided significantly greater IOP-lowering effects and better diurnal control than dorzolamide/timolol. At 8 a.m. measurements, bimatoprost lowered mean IOP -6.8 to -7.6 mm Hg from baseline, whereas combined timolol and dorzolamide lowered mean IOP -4.4 to -5 mm Hg from baseline ($p<0.001$). More patients achieved 8 a.m. IOP measurements less than 16 mm Hg with bimatoprost. In the dorzolamide/timolol group, taste perversion, and ocular burning and stinging with instillation occurred more frequently. Conjunctival hyperemia was more commonly reported with bimatoprost.

brimonidine 0.1% (Alphagan P) versus brimonidine 0.15% (Alphagan P)

In a 12-month, randomized, double-masked, multicenter, parallel-group, non-inferiority study, patients with glaucoma or ocular hypertension who were treated with brimonidine 0.15% twice daily were randomly assigned to continue brimonidine 0.15% ($n=102$) or to administer brimonidine 0.1% ($n=105$) twice daily for 12 months.¹⁸¹ Brimonidine 0.1% provided IOP-lowering that was non-inferior to brimonidine 0.15% at each of the 12 follow-up time points, and there were no statistically significant between-group differences at any time point. The most commonly reported adverse event was conjunctival hyperemia for both formulations. No significant differences in the incidence of adverse events were noted between the two.

brimonidine 0.15% (Alphagan P) versus brimonidine 0.2% (Alphagan)

In a three-month, multicenter, randomized, double-blind study of efficacy and safety, brimonidine 0.15% twice daily and brimonidine 0.2% twice daily demonstrated equivalent efficacy in reducing IOP in 407 patients with open-angle glaucoma or ocular hypertension.¹⁸² All patients were taking brimonidine 0.2% twice daily for at least six weeks prior to study entry and had IOP \leq 21 mm Hg. Patients were then randomized to brimonidine 0.15% or 0.2% for three months. No statistically significant differences were detected between the groups for IOP reduction or overall incidence of adverse effects. Authors concluded patients could be easily switched from brimonidine 0.2% twice daily to brimonidine 0.15% twice daily.

In a double-blind, randomized trial over 12 months with 764 open-angle glaucoma or ocular hypertension patients, brimonidine 0.15% given three times daily was found to be equally efficacious to brimonidine 0.2% three times daily in the reduction of IOP.¹⁸³ Diurnal IOP was measured at four time points between 8 a.m. and 5 p.m. at baseline, week six, and at months three, six, and 12. Difference in mean IOP between the brimonidine 0.15% and brimonidine 0.2% treatment groups was less than 1 mm Hg at all time points. Allergic conjunctivitis was 41 percent lower with brimonidine 0.15% compared to brimonidine 0.2%. Brimonidine 0.15% had higher scores of patient comfort and satisfaction, indicating preference of the brimonidine 0.15% formulation.

brimonidine 0.2% (Alphagan) and betaxolol suspension (Betoptic S)

Brimonidine 0.2% and betaxolol 0.25% suspension were compared in a multicenter, double-blind trial in 159 patients with elevated IOP.¹⁸⁴ Patients were randomized to brimonidine or betaxolol twice daily for four weeks. Mean IOP reductions after four weeks were -5.96 mm Hg with brimonidine and -5.07 mm Hg with betaxolol ($p=NS$). More brimonidine (64.2 percent) patients achieved a reduction of greater than 20 percent in IOP than betaxolol patients (47.4 percent; $p=0.033$). More patients treated with betaxolol reported hyperemia ($p=0.011$).

brimonidine/timolol (Combigan) and timolol (Timoptic) with brimonidine (Alphagan)

In two randomized, identical, double-blind, multicenter trials, 1,159 patients with ocular hypertension or glaucoma were treated with fixed brimonidine/timolol twice daily, brimonidine 0.2% three times a day, or timolol 0.5% twice daily for twelve months to evaluate IOP-lowering efficacy and safety of the three products.¹⁸⁵ The mean decrease from baseline IOP during 12-month follow-up was 4.4 to 7.6 mm Hg with fixed brimonidine/timolol, 2.7 to 5.5 mm Hg with brimonidine, and 3.9 to 6.2 mm Hg with timolol. Mean IOP reductions were significantly greater with fixed brimonidine/timolol compared with timolol at all measurements ($p\leq 0.002$) and compared to brimonidine at 8 a.m., 10 a.m., and 3 p.m. ($p<0.001$), but not at 5 p.m. The incidence of adverse events was lower in the fixed-combination group than in the brimonidine group ($p=0.006$) but higher than that in the timolol group ($p<0.001$). The rate of discontinuation for adverse events was 14.3 percent with brimonidine/timolol, 30.6 percent with brimonidine, and 5.1 percent with timolol.

brinzolamide (Azopt) and dorzolamide (Trusopt)

In a randomized, placebo-controlled, double-blind study, brinzolamide and dorzolamide were compared for efficacy, safety, and tolerability.¹⁸⁶ Patients were randomized to brinzolamide 1% two or three times daily, dorzolamide 2% three times daily, or placebo given three times daily. A total of 463 patients were randomized with available data for 409 patients for efficacy comparisons. Mean IOP changes after three months of active therapy were -3.4 to -4.1 mm Hg for brinzolamide twice daily, -4.1 to -4.8 mm Hg for brinzolamide three times daily, and -4.3 to -4.9 mm Hg for dorzolamide. All therapies were similar in efficacy in reducing IOP. Burning and stinging upon dose instillation were significantly higher with dorzolamide (12.2 percent) compared to brinzolamide (three percent). Two other studies have confirmed less discomfort with brinzolamide upon dose instillation compared to dorzolamide; however, pain may reduce over time with dorzolamide use.^{187,188}

dorzolamide/timolol (Cosopt) and timolol (Timoptic) with dorzolamide (Trusopt)

Investigators evaluated the use of the combination product versus the individual components in a two-part study. A total of 131 patients were randomized to dorzolamide/timolol or a topical carbonic anhydrase inhibitor and non-selective beta-blocker.¹⁸⁹ Patients underwent a one-month run-in period using the separate components. At baseline, the mean IOP readings were 18.4 and 21 mm Hg (peak and trough) for the patients randomized to the combination group. The mean IOP at baseline for the individual components were 17.6 and 19.8 mm Hg (peak and trough). After one month of treatment, the peak and trough in the combination groups were 17.6 and 19.5 mm Hg whereas the values were 17.3 and 19 mm Hg in the individual components group. Differences were not statistically significant, indicating in the clinical trial setting, administering the combination or individual agents provide the same effect on IOP. The other portion of the study enrolled 404 glaucoma patients on individual therapy with a beta-blocker and dorzolamide and converted these patients to the combination therapy. The baseline IOP prior to changing to the combination product was 19.4 mm Hg. After one month of combination therapy in a single container, the IOP was reduced by an additional 1.7 mm Hg ($p < 0.0001$). Of the population, 81 percent of eyes had IOP readings equal to or lower than the baseline readings.

latanoprost (Xalatan) and brimonidine (Alphagan)

Patients with uncontrolled glaucoma or ocular hypertension on beta-blockers were enrolled in a trial comparing brimonidine 0.2% twice daily and latanoprost 0.005% daily as adjunctive therapy over three months.¹⁹⁰ The prospective, multicenter, double-blind trial randomized 115 patients with mean baseline IOP of 21.3 mm Hg while on beta-blocker therapy. After one month of therapy, if at least 15 percent reduction in IOP at peak effect was not achieved, patients switched to the alternative therapy. Response rates (at least 15 percent reduction in IOP) and IOP reduction were similar between brimonidine and latanoprost at one month (4.88 mmHg [22.8 percent] with brimonidine and 5.01 mm Hg [23.5 percent] with latanoprost, $p = 0.798$). Of the patients with successful IOP reduction at one month, and continued on the initial study medication, the three-month mean IOP reductions were similar (-4.55 mm Hg reduction of IOP for brimonidine and -5.49 mm Hg reduction for latanoprost). There was no significant difference in the ability of brimonidine and latanoprost to maintain at least a 15 percent additional reduction in IOP for three months (28 of 38 patients on brimonidine versus 30 of 36 patients on latanoprost achieved at least a 15 percent IOP reduction at month three; $p = 0.314$). Significantly more patients on latanoprost complained of watery or teary eyes ($p = 0.025$) and cold extremities ($p = 0.012$).

Brimonidine 0.2% twice daily and latanoprost 0.005% once daily were compared in 127 patients with open-angle glaucoma or ocular hypertension in a randomized, three-month, multicenter, double-blind trial.¹⁹¹ The primary outcome measure was response rate, defined as the percentage of patients achieving at least 20 percent reduction in IOP from baseline to month three. The mean IOP after the medication washout period was 24.1 and 24.5 mm Hg in the latanoprost and brimonidine groups, respectively. The study excluded patients previously treated with either agent. Eighty percent of the brimonidine group and 74 percent of the latanoprost group achieved at least 20 percent reduction in IOP compared to baseline. The mean IOP reduction from baseline in each group at month three was -6.8 mm Hg with brimonidine and -6.5 mm Hg with latanoprost. More treatment-naïve patients treated with brimonidine achieved at least 20 percent decrease in IOP versus latanoprost (88 versus 59 percent; p=0.01). The previously treated patients achieved at least 20 percent reduction in IOP more frequently with latanoprost than brimonidine although the difference was not significant (88 versus 74 percent; p=NS).

latanoprost (Xalatan) and dorzolamide/timolol (Cosopt)

Two three-month, randomized, double-blind trials compared efficacy of dorzolamide 2%/timolol 0.5% twice daily and latanoprost 0.005% once daily in patients with ocular hypertension or open-angle glaucoma.¹⁹² Study A enrolled 256 patients from the U.S., and Study B enrolled 288 patients from Europe and Israel. Patients underwent a washout period and then were required to have baseline IOP greater than 24 mm Hg for study eligibility. Measurements of IOP occurred at 8 a.m., 10 a.m., 2 p.m., and 4 p.m.. After three months, mean daytime diurnal IOP was 18.9 mm Hg for the dorzolamide/timolol combination versus 18.4 mm Hg for latanoprost in Study A, and 17.4 mm Hg for the dorzolamide/timolol combination versus 17.5 mm Hg for latanoprost in Study B. Both therapies were well tolerated with only ocular stinging reported more frequently with dorzolamide/timolol. In a post-hoc analysis, both agents achieved a 40 percent reduction in IOP (target level) in 15 percent of the dorzolamide/timolol and 13 percent of the latanoprost groups.¹⁹³ In the patients with high baseline IOP (> 30 mm Hg), the mean IOP reduction was also similar (dorzolamide/timolol 12.5 mm Hg; latanoprost 12.6 mm Hg).

timolol (Timoptic) and timolol LA (Istalol)

Timolol LA contains potassium sorbate, which enhances the ocular bioavailability of timolol and reduces administration frequency to once daily.¹⁹⁴ The two formulations were compared to evaluate efficacy and safety in 332 patients with open-angle glaucoma or ocular hypertension.¹⁹⁵ In the multicenter, prospective, double-masked, parallel-group trial, patients were randomized to timolol LA 0.5% once daily or timolol twice daily for one year. Two hundred ninety patients completed the study. The baseline mean IOP was 25 mm Hg in both groups. At all measurements of IOP, the two groups were similar. A mean post-treatment IOP of 18 to 19 mm Hg at peak drug effect and 19 to 20 mm Hg just prior to redosing were observed. Mean reductions from baseline were 6 to 7 mm Hg (25.5 to 28.7 percent) at peak effect and 5 to 6 mm Hg (20.8 to 24.7 percent) at trough. Burning and stinging on instillation, which was mostly described as mild, was reported by 41.6 percent in the timolol LA group and 22.9 percent with timolol (p=0.001). No patients withdrew due to instillation adverse effects. Discontinuation rates were six percent and 4.2 percent for timolol LA and timolol, respectively.

travoprost (Travatan) and brinzolamide (Azopt) or timolol (Timoptic)

Efficacy and safety of timolol 0.5% and brinzolamide 1% when given in combination with travoprost 0.004% were compared in 192 patients with ocular hypertension or primary open-angle glaucoma.¹⁹⁶ In the double-blind, randomized study, patients were started on travoprost every evening for four weeks and then were randomized to timolol or brinzolamide given twice daily. IOP measurements were recorded at the end of travoprost monotherapy and then 12 weeks after receiving the combination therapy. There were no differences between the groups for IOP reductions from baseline for each time point of IOP measurement throughout the day or for the mean diurnal IOP (18.1 mm Hg for both groups). No significant differences were observed for adverse effects; the most common was conjunctival hyperemia with 16 percent of brinzolamide-treated patients and six percent with timolol-treated patients (p=0.06).

travoprost (Travatan) and timolol (Timoptic)

A total of 426 patients who had open-angle glaucoma or ocular hypertension and were inadequately controlled on timolol 0.5% twice daily were randomized in a double-masked trial to receive travoprost 0.0015% or 0.004% or placebo in the evening.¹⁹⁷ Patients were followed for six months. The IOP was lowered an additional -5.7 to -7.2 mm Hg and -5.1 to -6.7 mm Hg in the travoprost 0.004% and 0.0015% concentrations, respectively. These changes were significantly different from the vehicle group (-1.3 to -2.8 mm Hg, p≤0.0001). Average hyperemia scores ranged from trace to mild for all treatment groups.

Two double-blind, randomized studies, one six-month (n=605) and one nine-month (n=573), evaluated travoprost 0.0015% and 0.004% once daily with timolol 0.5% twice daily in patients with open-angle glaucoma or ocular hypertension.^{198,199} Enrollment required baseline IOP between 24 and 36 mm Hg in at least one eye. Travoprost 0.0015% and 0.004% significantly lowered mean IOP measurements more than timolol in both studies. In the nine-month study, travoprost 0.004% produced a significantly greater reduction in the mean IOP from baseline than timolol (-8 to -8.9 mm Hg versus -3.6 to -7.9 mm Hg; p≤0.00001). Hyperemia was more common with travoprost. In the six-month study, 29.2 percent of travoprost 0.0015% patients experienced hyperemia compared to 42.8 percent of travoprost 0.004% and 8.9 percent of timolol patients. In the nine-month study, timolol was better tolerated than either strength of travoprost.

travoprost (Travatan), latanoprost (Xalatan), and timolol (Timoptic)

A total of 801 patients with open-angle glaucoma or ocular hypertension were randomized in a double-masked trial to receive travoprost 0.0015%, 0.004%, latanoprost 0.005%, or timolol 0.5% for a period of 12 months.²⁰⁰ Patients receiving travoprost or latanoprost received once daily administration; patients receiving timolol had twice-daily administrations. Travoprost was equal or superior to latanoprost and superior to timolol, with mean IOP over visits and time of day ranging from 17.9 to 19.1 mm Hg (travoprost 0.0015%), 17.7 to 19.1 mm Hg (travoprost 0.004%), 18.5 to 19.2 mm Hg (latanoprost), and 19.4 to 20.3 mm Hg (timolol). Travoprost was associated with good reductions in IOP in the black population. Response rates, considered to be at least 30 percent or greater IOP reduction from diurnal baseline or IOP 17 mm Hg or less, were 49.3 and 54.7 percent for travoprost 0.0015% and 0.004%, respectively, compared with 49.6 percent for latanoprost and 39 percent for timolol. Iris pigmentation change was observed in five percent of patients receiving travoprost 0.0015%, 3.1 percent of patients receiving travoprost 0.004%, 5.2 percent of patients receiving latanoprost, and none of the patients receiving timolol.

In two double-blind, randomized studies with a total of 1,381 patients with open-angle glaucoma or ocular hypertension, travoprost, latanoprost, and timolol were evaluated for efficacy.²⁰¹ Patients were randomized to travoprost 0.004% daily, latanoprost 0.005% daily, or timolol 0.5% twice daily. The mean IOP was significantly lower in Blacks treated with travoprost, and travoprost was superior to latanoprost in Blacks. Timolol lowered the mean IOP to a greater extent in non-Black patients.

A randomized, double-blind, six-week trial compared the tolerability and efficacy of travoprost 0.004% once daily (n=155) and latanoprost 0.005% once daily (n=147) in 302 patients with open-angle glaucoma or ocular hypertension in Latin America.²⁰² Following six weeks of double-blinded treatment, all patients were treated with travoprost 0.004% once daily for an additional six weeks. Measurements of IOP were recorded at 5 p.m. (approximately 20 hours after drug instillation) at weeks one, two, four, six, eight, and 12. Mean IOP values were not significantly different between the travoprost and latanoprost groups at baseline (24.7 versus 24.2 mm Hg) or six weeks; however, the between-group difference in reductions from baseline in pooled IOP during the masked phase of the study was statistically significant (-8.3 versus -7.5 mm Hg; p=0.009). At weeks six and 12, mean IOP levels were 16.1 and 16.2 mm Hg, respectively, in the travoprost group and 16.4 and 16.1 mm Hg in the group that was switched from latanoprost to travoprost (all p=NS). Hyperemia was the most common ocular adverse effect with 26.9 percent of blinded travoprost, 12.2 percent of latanoprost, and 5.3 percent of open-label travoprost patients affected.

travoprost (Travatan), latanoprost (Xalatan), and bimatoprost (Lumigan)

Travoprost 0.004%, bimatoprost 0.03%, and latanoprost 0.005% daily were compared for efficacy, safety, and tolerability over 12 weeks with 411 patients with open-angle glaucoma or ocular hypertension.²⁰³ The study was a multicenter, double-blind, randomized clinical trial based in the US. Baseline IOP after washout was at least 23 mm Hg in one or both eyes. Patients were randomized to one of the three therapies and followed for reduction in IOP and hyperemia. After 12 weeks, IOP was measured at 8 a.m., 12 p.m., 4 p.m., and 8 p.m.. IOP readings were similar at all time points for all drugs (16-17.6 mm Hg). Latanoprost patients reported fewer ocular adverse effects compared to bimatoprost. Average hyperemia scores were lower with latanoprost compared to bimatoprost (p=0.001).

A study enrolled 44 patients with glaucoma or ocular hypertension in a randomized, double-blind crossover study comparing the effects of latanoprost 0.005%, travoprost 0.004%, and bimatoprost 0.03% on the circadian IOP.²⁰⁴ Patients were treated with each agent for one month, each given in a random sequence with a 30-day washout period between drugs. IOP was recorded at eight time points in a 24-hour period at baseline and following treatment with each agent. All three agents significantly reduced IOP compared to baseline. The mean IOP reductions were similar among the agents with no significant differences. All agents tested had greater effect during the daytime than at night.

travoprost (Travatan) and travoprost (Travatan Z)

The safety and efficacy of travoprost 0.004% without benzalkonium chloride (BAC) and travoprost 0.004% (Travatan) were compared in 790 patients with open-angle glaucoma or ocular hypertension.²⁰⁵ In the double-blinded, randomized, parallel group trial, adult patients received one of the formulations of travoprost as one drop once daily. IOP measurements at 8 a.m., 10 a.m., and 4 p.m. were taken at three visits over three months. Mean IOP reductions across all study visits and times ranged from 7.3 to 8.5 mm Hg for travoprost 0.004% without BAC and from 7.4 to 8.4 mm Hg for travoprost 0.004% with BAC (p=NS). Adverse events were

similar between the two groups with the exception of hyperemia which occurred in 6.4 percent with travoprost without BAC and 9 percent in travoprost (Travatan).

Meta-Analyses

A meta-analysis evaluated nine studies of the prostaglandin analogs for the management of glaucoma or ocular hypertension.²⁰⁶ A total of 1,318 patients were evaluated in the analysis. Patients treated with travoprost and bimatoprost had lower IOP levels at the end of follow-up (-0.98 mmHg [95% CI, -2.08; 0.13; p=0.08] and -1.04 mmHg [95% CI, -2.11;0.04; p=0.06], respectively) than those treated with latanoprost. In another meta-analysis, travoprost 0.004% had equivalent efficacy to bimatoprost and latanoprost in a total of 12 studies. Travoprost had greater efficacy in reducing IOP than timolol.²⁰⁷

Another systematic review evaluated the IOP lowering efficacy and tolerability of the prostaglandin analogs in eight trials with 1,610 patients with ocular hypertension or primary open-angle glaucoma.²⁰⁸ The main efficacy outcome measures were IOP measurements taken at 8 AM, noon, 4 PM, and 8 PM and the change at three months from baseline and tolerability. IOP change from baseline was statistically significantly greatest with bimatoprost, compared with latanoprost at all time points (8 a.m. p=0.05, noon p<0.001, 4 p.m. p=0.003, and 8 p.m. p=0.004). Latanoprost and travoprost were comparable in their ability to reduce IOP at all time points (p≤0.82). Tolerability assessed by the incidence of conjunctival hyperemia. The incidence of hyperemia was less with latanoprost and travoprost [latanoprost versus bimatoprost: relative risk=0.59; p<0.001; 95% CI, 0.50-0.69; travoprost versus bimatoprost: relative risk=0.84; p=0.05; 95% CI, 0.70-1.00].

A meta-analysis evaluated the IOP reduction of several agents in this class.²⁰⁹ A total of 27 articles with 6,953 patients with trough IOP readings and 6,841 patients with peak IOP readings were included. Over 85 percent of patients had primary open-angle glaucoma or ocular hypertension. The greatest IOP reductions were reported with timolol, latanoprost, travoprost, and bimatoprost, with peak reductions of 27 to 33 percent and trough reductions of 26 to 29 percent from baseline.

A meta-analysis of 13 trials (n=1,302) evaluated the efficacy and tolerability of bimatoprost and latanoprost.²¹⁰ Bimatoprost was associated with greater reductions in IOP in the morning compared to latanoprost at one, three, and six months. Bimatoprost was associated with significantly greater frequency of hyperemia than latanoprost. Another meta-analysis of 13 trials with 2,222 patients with ocular hypertension or glaucoma evaluated the incidence of conjunctival hyperemia among the three prostaglandin analogs.²¹¹ The combined results showed that latanoprost produced lower occurrence of conjunctival hyperemia than both travoprost (OR=0.51; 95% CI, 0.39 to 0.67, p<0.0001) and bimatoprost (OR=0.32; 95% CI, 0.24 to 0.42, p<0.0001).

Summary

Selection of a wide variety of agents for the treatment of glaucoma is important, as patients often require a combination of therapies to achieve adequate control of elevated IOP. Currently, no guidelines suggest any one class should be used as first line; however, safety and tolerability of the medications should play a role in product selection. The target IOP reductions are typically 20 to 30 percent, and even up to 50 percent, below baseline. Beta-blockers, carbonic anhydrase inhibitors, and prostaglandin analogs are the mainstays of therapy.

Brimonidine (Alphagan / P), carbonic anhydrase inhibitors, and beta blockers are capable of decreasing IOP by 20 to 25 percent. No differences between brimonidine (generics, Alphagan

P) products are known at this time. Dorzolamide (Trusopt) may cause more stinging upon application compared to brinzolamide (Azopt). Timolol LA (Istalol) also may cause more stinging than timolol products that are applied more frequently. In clinical trials, prostaglandin agonists were at least as effective as agents from other classes, and frequently showed superior efficacy compared to timolol (Timoptic / XE).

Prostaglandin analogs may be the most effective drugs, achieving up to 30 percent reductions in IOP. Most head-to-head comparative studies are performed in small patient populations. Bimatoprost (Lumigan), latanoprost (Xalatan), and travoprost (Travatan, Travatan Z) have been shown to have better efficacy compared to timolol. The prostaglandin analogs have also been shown to have an additive effect when used with beta-blocker therapy. Side effect profiles of the prostaglandin analogs are different than the beta-blocker agents used for glaucoma treatment.

Direct-acting miotics including pilocarpine are second or third line therapy due to frequent administration and lower tolerability. Apraclonidine (Iopidine) is used in short-term treatment of glaucoma, often in combination with other IOP-reducing medications.

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