



Ophthalmics, Glaucoma Agents Therapeutic Class Review (TCR)

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FDA-APPROVED INDICATIONS¹

Drug	Manufacturer	Reduction of elevated IOP in ocular hypertension	Reduction of elevated IOP in open-angle glaucoma
Beta-blockers			
betaxolol (Betoptic S [®]) ²	generic, Alcon	X	X
carteolol ³	generic	X	X
levobunolol ⁴	generic	X	X
timolol (Betimol [®]) ⁵	Oak/Akorn	X	X
timolol (Timoptic [®] , Timoptic in Ocudose [®]) ^{6,7}	generic, Valeant/Bausch	X	X
timolol ER* (Timoptic XE [®]) ⁸	generic*, Valeant/Bausch	X	X
timolol ER† (Timolol GSF) ⁹	Sandoz	X	X
timolol long-acting (LA) (Istalol [®]) ¹⁰	generic, Valeant	X	X
Carbonic Anhydrase Inhibitors			
brinzolamide (Azopt [®]) ¹¹	Alcon	X	X
dorzolamide (Trusopt [®]) ¹²	generic, Merck	X	X
Cholinesterase Inhibitor			
echothiophate iodide‡ (Phospholine Iodide [®]) ¹³	Pfizer	X	X
Miotic, Topical			
pilocarpine§ (Isopto Carpine [®]) ¹⁴	generic, Alcon	X	X
Prostaglandin Analogs			
bimatoprost (Lumigan [®]) ¹⁵	generic, Allergan	X	X
latanoprost emulsion¶ (Xelpros [™]) ¹⁶	Sun	X	X
latanoprost solution (Xalatan [®]) ¹⁷	generic, Pharmacia/Pfizer	X	X
latanoprostene bunod (Vyzulta [®]) ¹⁸	Valeant	X	X
tafluprost (Zioptan [®]) ¹⁹	Akorn	X	X
travoprost (Travatan [®] Z) ²⁰	Alcon	X	X

ER = extended-release; IOP = intraocular pressure

* Authorized generic is available.

† Timolol GFS (timolol gel forming solution) was FDA-approved under a 505(b)(2) pathway, in which approval relied, at least in part, on data not developed by the applicant.^{21,22}

‡ Echothiophate iodide (Phospholine Iodide) is also indicated for the treatment of accommodative esotropia.²³

§ Pilocarpine is also indicated for the management of acute-angle-closure glaucoma, for the prevention of postoperative elevated IOP associated with laser surgery, and for the induction of miosis.

¶ FDA-approval was under the 505(b)(2) pathway, in which at least some of the safety and efficacy data was from clinical studies not conducted by or for the applicant.

FDA-Approved Indications (continued)

Drug	Manufacturer	Reduction of elevated IOP in ocular hypertension	Reduction of elevated IOP in open-angle glaucoma
Rho Kinase Inhibitor			
netarsudil (Rhopressa®) ²⁴	Aerie	X	X
Sympathomimetics			
apraclonidine (Iopidine®) ²⁵	generic, Alcon	X [¶]	X [¶]
brimonidine* (Alphagan P®) ^{26,27}	generic, Allergan	X	X
Combination Products			
brimonidine/brinzolamide (Simbrinza®) ²⁸	Alcon	X	X
brimonidine/timolol (Combigan®) ²⁹	Allergan	X ^{**}	X ^{**}
dorzolamide/timolol (Cosopt®, Cosopt PF®) ^{30,31}	generic, Akorn	X ^{**}	X ^{**}
netarsudil/latanoprost [†] (Rocklatan™) ³²	Aerie	X	X

* Authorized generic available

¶ 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 IOP rises significantly.³³ 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.³⁴

|| FDA-approval was under the 505(b)(2) pathway, in which at least some of the safety and efficacy data was from clinical studies not conducted by or for the applicant.

** Indicated as adjunctive or replacement therapy

Preservative-free Timoptic in Ocudose may be used when a patient is sensitive to the preservative in timolol maleate ophthalmic solution (Betimol, Timoptic), benzalkonium chloride, or when use of a preservative-free topical medication is advisable.

Cosopt PF is a preservative-free formulation and provided in single dose vials; thus, it can be used in patients that are allergic or sensitive to preservatives within dorzolamide/timolol (Cosopt).³⁵

Tafluprost (Zioptan) is a preservative-free formulation provided in single use containers.³⁶

Latanoprost solution (Xalatan) contains benzalkonium chloride 0.02% as a preservative, while potassium sorbate 0.47% is the preservative agent in latanoprost emulsion (Xelpros).

OVERVIEW

Approximately 2.7 million people in the United States (U.S.) suffer from glaucoma. It is the second most common cause of permanent blindness in the U.S. and the most common cause of blindness among African Americans and Hispanics.^{37,38}

Increased 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. However, some patients with glaucoma have normal IOP, and many patients with elevated IOP do not have glaucoma. IOP alone 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. Risk factors for the development of glaucoma include elevated IOP, advancing age (> 60 years), family history of glaucoma, and African American (> age 40 years) or Hispanic descent.^{39,40,41,42,43} African Americans have a higher prevalence compared to Caucasians; however, Caucasians have a steeper rise in open-angle glaucoma associated with advancing age.^{44,45} In addition, people of Asian descent and Native Alaskans are at higher risk for angle-closure glaucoma.⁴⁶

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.⁴⁷ Topical ocular hypotensive agents can delay or prevent the development of primary open-angle glaucoma in some patients.⁴⁸

The goal of treatment is to maintain the IOP in a range at which loss of visual field is unlikely to significantly affect a patient's health related quality of life over their lifetime.⁴⁹ An initial target pressure is at least 25% lower than pretreatment IOP. However, target pressure is an estimate and should be individualized based on disease course; lower IOP targets are reasonable in patients with more severe optic nerve damage. Medical therapy is the most common initial intervention to lower IOP. Medication classes used in the management of glaucoma include beta-blockers, miotics, sympathomimetics, topical and oral carbonic anhydrase inhibitors, and prostaglandin F₂α 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 (AAO) 2015 preferred practice patterns, prostaglandin analogs are the most frequently prescribed initial eye drops to lower IOP due to their efficacy, safety profile, and once-daily regimen.^{50,51} Adequate treatment of glaucoma requires a high level of adherence to therapy. Use of the cholinesterase inhibitor echothiophate iodide (Phospholine Iodide) is not included in the 2015 preferred practice patterns. Netarsudil (Rhopressa) and netarsudil/latanoprost (Rocklatan) were not available at the time the AAO preferred practice patterns were developed.

PHARMACOLOGY^{52,53,54,55,56}

Drug	Decreased aqueous humor production	Increased trabecular outflow	Increased uveoscleral outflow
Beta-blockers			
betaxolol (Betoptic S)	X		
carteolol	X		
levobunolol	X		
timolol (Betimol, Timolol GFS, Timoptic, Timoptic XE, Timoptic in Ocudose, Istalol)	X		
Carbonic Anhydrase Inhibitors			
brinzolamide (Azopt)	X		
dorzolamide (Trusopt)	X		
Cholinesterase Inhibitors			
echothiophate iodide (Phospholine Iodide)		X	
Miotics, Topical			
pilocarpine		X	
Prostaglandin F2α Analogs			
bimatoprost (Lumigan)		X	X
latanoprost (Xalatan, Xelpros, Rocklatan)			X
latanoprostene bunod (Vyzulta)		X	X
tafluprost (Zioptan)			X
travoprost (Travatan Z)		X	X
Rho Kinase Inhibitor			
netarsudil (Rhopressa, Rocklatan)		X	
Sympathomimetics			
apraclonidine (Iopidine)	X	X	X
brimonidine (Alphagan P)	X		X
Combination Products			
brimonidine/brinzolamide (Simbrinza)	X		X
brimonidine/timolol (Combigan)	X		X
dorzolamide/timolol (Cosopt, Cosopt PF)	X		

PHARMACOKINETICS^{57,58,59,60,61,62,63,64,65,66,67,68,69,70,71,72,73,74,75,76,77,78,79,80,81}

Systemic absorption occurs with topical beta-blockers, prostaglandin analogs, topical ophthalmic sympathomimetics, topical carbonic anhydrase inhibitors, and topical direct-acting miotics, including pilocarpine. Potential for systemic adverse effects exists for these classes.

Brimonidine (Alphagan P) 0.1% and 0.15% ophthalmic solutions contain Purite 0.005% as the preservative. Brimonidine 0.2%, using benzalkonium chloride, has been associated with a higher incidence of allergic reactions in clinical trials.⁸²

Echothiophate iodide (Phospholine Iodide) contains the preservatives chlorobutanol and boric acid. The product is reconstituted under aseptic technique by a pharmacist. Long-term administration of echothiophate iodide will result in decreased cholinesterase concentrations. To prevent systemic

absorption, patients should apply pressure to the inner canthus for 1 to 2 minutes following administration. Echothiophate iodide is protein bound and inactivated by phosphorylphosphatases before being excreted in the urine.

Latanoprost emulsion (Xelpros) uses a proprietary swollen micelle microemulsion technology to increase the solubility of latanoprost, which typically requires benzalkonium chloride to remain in solution.⁸³

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

Drug	Pro-drug	Metabolism	Excretion (%)	Onset (hours)	Maximum effect (hours)
bimatoprost (Lumigan)	No	Liver – many metabolites	Urine: 67 Feces: 25	4	8-12
latanoprost (Xalatan, Xelpros, Rocklatan)	Yes – hydrolyzed by esterases to active free acid	Liver – 2 metabolites	Urine: 88	3-4	8-12
latanoprostene bunod (Vyzulta)	No	Liver – 2 metabolites	nr	1-3	11-13
tafluprost (Zioptan)	Yes – hydrolyzed by esterases to active free acid	Liver – 10 metabolites	nr	2-4	12
travoprost (Travatan Z)	Yes – hydrolyzed by esterases to active free acid	Liver – inactive metabolites	Rapid systemic elimination	2	After 12

nr = not reported

Travatan Z contains travoprost 0.004% and the preservative, sofZia™. SofZia contains boric acid, propylene glycol, sorbitol, and zinc chloride; the generic travoprost preparation contains benzalkonium chloride as the preservative. Tafluprost (Zioptan) is preservative-free.

Netarsudil (Rhopressa) contains boric acid as a preservative. Systemic exposure of netarsudil is minimal, as it is metabolized via esterases in the eye.

Timolol maleate ophthalmic solution (Betimol, Timoptic) contains benzalkonium chloride. Timolol ophthalmic gel-forming solution (Timolol GFS, Timoptic XE) contains benzododecinium bromide as the preservative. Timolol LA (Istalol) contains potassium sorbate, which enhances the ocular bioavailability of timolol and reduces administration frequency to once daily.⁸⁴

Latanoprost solution (Xalatan) and netarsudil/latanoprost (Rocklatan) contain benzalkonium chloride 0.02% as a preservative, while potassium sorbate 0.47% is the preservative agent in latanoprost emulsion (Xelpros).

Brimonidine is extensively metabolized by the liver; both the drug and its metabolites are eliminated in the urine.

Cosopt PF (dorzolamide/timolol) is preservative-free.

CONTRAINDICATIONS/WARNINGS^{85,86,87,88,89,90,91,92,93,94,95,96,97,98,99,100,101,102,103,104,105,106,107,108,109}

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

Beta-blockers, including the combination products, are generally contraindicated in patients with sinus bradycardia, second or third degree atrioventricular block, cardiogenic shock, overt cardiac failure, a history of bronchial asthma, or severe chronic obstructive pulmonary disease (COPD).¹¹⁰

Apraclonidine (Iopidine) is contraindicated in patients receiving monoamine oxidase (MAO) inhibitors.

Brimonidine (Alphagan P, Combigan, Simbrinza) is contraindicated in neonates and children less than 2 years of age.

Echothiophate iodide (Phospholine Iodide) is contraindicated in patients with active uveal inflammation and most cases of angle-closure glaucoma without iridectomy, due to the possibility of increasing angle block.

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

In general, agents in this review are contraindicated in those patients with a history of hypersensitivity to any component of the medication.

Warnings

In March 2016, the FDA warned that eye drop bottles that have loose plastic safety seals or tamper-evident rings below the bottle cap may fall onto the eye when the product is used. The FDA will identify all relevant products and will require a change in the packaging design.¹¹¹

Beta-blockers

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 death associated with cardiac failure.¹¹²

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 be used when prescribing beta-blocker therapy in patients with mild to moderate COPD or current or history of bronchospastic disease. Using agents other than beta-blockers may be more appropriate for patients with these concurrent disease states.

Beta-adrenergic receptor inhibitors should be administered with caution in patients subject to hypoglycemia or patients with diabetes (especially those with labile diabetes) who are receiving insulin

or oral hypoglycemic agents. Beta-adrenergic receptor inhibitors may mask the signs and symptoms of acute hypoglycemia.

Beta-blockers may mask certain clinical signs of hyperthyroidism, such as tachycardia. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta-blockers that might precipitate a thyroid storm.

Beta-adrenergic blockade may potentiate muscle weakness consistent with myasthenic symptoms such as diplopia, ptosis, and generalized weakness.

Levobunolol and other ophthalmic beta-blockers may increase risk of hypotension through the impairment of compensatory tachycardia.

Some patients receiving beta blockers have experienced protracted, severe hypotension during anesthesia. Gradual withdrawal of beta-blocker should be considered in prior to elective surgery.

Betaxolol (Betoptic S) must be used with caution in patients with vascular insufficiency and should be discontinued if signs or symptoms of decreased cerebral blood flow or Raynaud's phenomenon develop.

Betaxolol (Betoptic S) has little or no effect on the pupil; it should therefore not be used alone for the treatment of angle-closure glaucoma.

Choroidal detachment after filtration procedures has been reported with beta blockers.

Carbonic Anhydrase Inhibitors

Brinzolamide (Azopt, Simbrinza) and dorzolamide (Trusopt) are topically administered sulfonamides that are 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, and blood dyscrasias (e.g., agranulocytosis, aplastic anemia). Sensitization may recur when a sulfonamide is re-administered by any route. If signs of hypersensitivity develop, discontinue the medication.

Corneal edema may occur in patients with low endothelial cell counts who are on brinzolamide (Azopt, Simbrinza) or dorzolamide (Trusopt).

Brinzolamide (Azopt) and brinzolamide/brimonidine (Simbrinza) have not been studied in patients with acute angle-closure glaucoma.

Cholinesterase Inhibitor

Echothiophate iodide (Phospholine Iodide) should be used with caution with concomitant systemic anticholinesterase inhibitors due to possible additive effects. In patients treated with echothiophate iodide, succinylcholine associated with anesthesia should be used with great care, if at all, due to possible respiratory or cardiovascular collapse.

Discontinue echothiophate iodide if the patient experiences cardiac abnormalities. Use caution in patients with market vagotonia, asthma, gastric spasticity, peptic ulcer, marked bradycardia and hypotension, recent myocardial infarction, epilepsy, parkinsonism, or history of retinal detachment.

Temporarily stop echothiophate iodide therapy if any of the following occur: salivation, urinary incontinence, diarrhea, profuse sweating, muscle weakness, or respiratory difficulties.

Patients take precautions such as respiratory masks, frequent hand washings, and clothing changes, during exposure to pesticides.

Miotic

Pilocarpine-induced miosis may cause difficulty in dark adaptation. Patients should be advised to exercise caution in night driving and other hazardous occupations in poor illumination.

Prostaglandin Analogs

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% solution (Xalatan) once daily has been evaluated for 5 years for safety and efficacy in patients with primary open-angle or exfoliation glaucoma.¹¹³ A total of 519 patients started the 3-year open-label, prospective study with 380 patients participating in the 2-year extension phase. After 5 years, iris pigmentation was observed in a small number of patients. The onset occurred within the first 24 months in 94% of patients who experienced iris pigmentation changes. The rate of progression of pigmentation change decreased over time. The mean IOP was reduced by 25% from baseline throughout the observation period of 5 years with 70% of patients not requiring a change in therapy.

Onset of iris pigmentation occurs in the first year of bimatoprost (Lumigan) therapy for the majority of patients. For those with iris pigmentation associated with bimatoprost, increasing iris pigmentation has been observed for up to 5 years. The iris pigmentation did not affect the incidence or severity of other adverse effects. The effects of increased pigmentation beyond 5 years are not known.

All agents may gradually change eyelashes by increasing length, thickness, pigmentation, and number of lashes. Changes on eyelashes are reversible if the prostaglandin is discontinued. These changes are especially important when medication is administered to 1 eye only.

Prostaglandin analogs should be used with caution in patients with a history of intraocular inflammation (e.g., iritis/uveitis) as inflammation can be exacerbated and should generally not be used in patients with active intraocular inflammation. Macular edema, including cystoid macular edema, has been reported during therapy with prostaglandin analogs. Use prostaglandin F₂α analogs with caution in aphakic patients, in pseudophakic patients with a torn posterior capsule, or in patients with known risk factors for macular edema.

Reactivation of herpes simplex keratitis has been reported during treatment with latanoprost (Xalatan, **Xelpros**, **Rocklatan**). Use with caution in patients with a history of herpetic keratitis.

Bimatoprost (Lumigan) has not been evaluated for the treatment of angle-closure, inflammatory, or neovascular glaucoma.

Sympathomimetics

Although apraclonidine (Iopidine) and brimonidine (Alphagan P, Simbrinza) had minimal effect on the blood pressure of patients in clinical studies, caution should be exercised in treating patients with

severe cardiovascular disease, cerebral or coronary insufficiency, Raynaud's phenomenon, or thromboangiitis obliterans. Brimonidine should also be used with caution in patients with depression or orthostatic hypotension.

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. No evidence of cross-reactive allergic responses to brimonidine in patients with known allergy to apraclonidine has been found.¹¹⁴

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.

Ocular hypersensitivity reactions with increased intraocular pressure have been reported with brimonidine (Combigan).

The addition of apraclonidine 0.5% as part of a patient's maximally tolerated medical therapy may not provide additional benefit if 2 aqueous humor-suppressing drugs, such as beta-blockers and carbonic anhydrase inhibitors, are already being used. 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 1 month. This warning is not associated with apraclonidine 0.1% solution.

DRUG INTERACTIONS^{115,116,117,118,119,120,121,122,123,124,125,126,127,128,129,130,131,132,133,134,135,136,137,138,139,140}

Beta-blockers

Ophthalmic beta-blockers given with oral 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 2 beta-blockers for ophthalmic purposes is not recommended.

Potentiated systemic beta-blockade (e.g., decreased heart rate) has been reported during combined treatment with CYP2D6 inhibitors (e.g., quinidine, selective serotonin reuptake inhibitors [SSRIs]) and timolol [Betimol, Istalol, Timolol GFS, Timoptic]).

Close observation of patients is recommended when a beta-adrenergic receptor inhibitor is administered to patients receiving catecholamine-depleting drugs (e.g., reserpine). This is due to possible additive effects and hypotension and/or bradycardia which may result in vertigo, syncope, or postural hypotension.

Carbonic Anhydrase Inhibitors

There is a potential for an additive effect on the known systemic effects of carbonic anhydrase inhibition in patients receiving an oral carbonic anhydrase inhibitor and brinzolamide (Azopt, Simbrinza) or dorzolamide (Trusopt, Cosopt). Concurrent use is not recommended.

Cholinesterase Inhibitor

Other cholinesterase inhibitors such as succinylcholine or organophosphate and carbamate insecticides effects are potentiated by echothiophate iodide (Phospholine Iodide). Patients taking systemic anticholinesterase treatment should be made aware of the possible additive effects.

Miotic

Cyclopentolate may diminish the therapeutic effect of pilocarpine ophthalmic preparation; monitor therapy with concurrent use.

Use of pilocarpine with other drugs with anticholinergic effect should be avoided due to a potential reduction of the therapeutic effect of either agent.

Prostaglandin Analogs

Ophthalmic products containing thimerosal should be administered at least 5 minutes apart from latanoprost (Xalatan, **Xelpros**, **Rocklatan**) as precipitation has been reported. Using a combination of 2 or more prostaglandins or prostaglandin analogs is not recommended.

Rho Kinase Inhibitor

Drug interaction studies for netarsudil (Rhopressa) have not been conducted; they are not included in prescribing information for netarsudil.

Sympathomimetics

Specific drug interaction studies have not been performed with brimonidine (Alphagan P, Simbrinza) 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 co-administration of ophthalmic sympathomimetics 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 or brimonidine can lead to a diminished IOP-lowering effect. Caution is advised in patients taking TCAs which can affect the metabolism and uptake of circulating amines.

Apraclonidine or brimonidine should not be used in patients receiving MAO inhibitors.

ADVERSE EFFECTS^{141,142,143,144,145,146,147,148,149,150,151,152,153,154,155,156,157,158,159,160,161,162,163,164,165,166}

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
Beta-blockers												
betaxolol (Betoptic S)	nr	*	nr	*	*	*	*	*	*	*	*	
carteolol	*	25	*	nr	25	nr	nr	nr	*	25	*	
levobunolol	*	nr	*	nr	30	nr	nr	nr	nr	nr	*	
timolol (Betimol, Timoptic)	*	nr	*	*	12.5	*	*	*	nr	*	*	
timolol gel forming solution (Timolol GFS, Timoptic XE)	*	nr	1-5	*	12.5	1-5	1-5	1-5	nr	1-5	30	
timolol LA (Istalol)	*	nr	*	*	38	*	4-10	*	nr	*	4-10	
Carbonic Anhydrase Inhibitors												
brinzolamide (Azopt)	1-5	nr	< 1	1-5	nr	1-5	1-5	1-5	nr	< 1	5-10	5-10: bitter taste
dorzolamide (Trusopt) ¹⁶⁷	nr	1-5	nr	1-5	nr	nr	nr	*	1-5	1-5	1-5	25: bitter taste
Cholinesterase Inhibitor												
echothiophate iodide (Phospholine Iodide)	nr	*	nr	nr	*	nr	nr	nr	nr	*	*	
Miotic, Topical												
pilocarpine	nr	nr	nr	nr	*	nr	nr	*	*	*	*	

Adverse effects are reported as a percentage. Adverse effects data are obtained from package information and should not be considered comparative or all inclusive. * = 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
Prostaglandin Analogs												
bimatoprost (Lumigan)	1-10	25-45	1-10	1-10	1-10	1-10	> 10	1-10	1-10	1-10	1-10	> 10 eyelash growth cataracts 1-10%
latanoprost emulsion (Xelpros)	nr	15	*	3	55	2	5	55	nr	nr	4	eyelash growth
latanoprost solution (Xalatan)	*	8	*	3	7-9	13	8	3	2	4	8	eyelash growth
latanoprostene bunod (Vyzulta)	nr	6	nr	nr	nr	*	nr	3	nr	nr	*	eyelash growth eyelash darkening
tafluprost (Zioptan)	nr	4-20	1-5	3	7	nr	5	3	nr	nr	2	3: eyelash growth eyelash darkening cataracts
travoprost (Travatan Z)	1-4	30-50	1-4	1-4	nr	5-10	5-10	5-10	1-4	1-4	1-10	3: eyelash growth cataracts
Rho Kinase Inhibitor												
netarsudil mesylate (Rhopressa)	nr	53	nr	nr	nr	nr	nr	20	nr	5-10	5-10	20: corneal verticillata, conjunctival hemorrhage
Sympathomimetics												
apraclonidine 0.5% (Iopidine)	< 1	5-15	1-5	1-5	*	1-5	5-15	< 1	< 1	1-5	1-5	10: oral dryness; hypersensitivity*
apraclonidine 1% (Iopidine)	nr	nr	nr	*	*	*	*	nr	nr	nr	*	hypersensitivity*
brimonidine (Alphagan P)	1-4	10-20	10-20	1-4	5-9	1-4	10-20	1-4	1-4	1-4	5-9	5-9: oral dryness
brimonidine 0.2%	3-9	3-30	10-30	3-9	10-30	10-30	10-30	3-9	3-9	3-9	10-30	10-30: oral dryness

Adverse effects are reported as a percentage. Adverse effects data are obtained from package information and should not be considered comparative or all inclusive.
* = 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
Combination Products												
brimonidine/brinzolamide (Simbrinza)	*	*	*	*	*	*	*	*	*	*	3-5	3-5: dysgeusia, eye irritation, dry mouth
brimonidine/timolol (Combigan)	1-5	5-15	5-15	1-5	5-15	1-5	5-15	1-5	*	*	1-5	5-15: conjunctival folliculosis
dorzolamide/timolol (Cosopt, Cosopt PF)	1-5	5-15	1-5	1-5	*	1-5	5-15	1-5	< 1	1-5	5-15	< 30: taste perversion
netarsudil/latanoprost (Rocklatan)	nr	59	nr	*	*	*	5-8	*	*	5-8	5-8	eyelash growth eyelash, eyelid darkening corneal verticillata (15%), conjunctival hemorrhage (11%)

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

Periorbital and lid changes, including deepening of the eyelid sulcus, abnormal hair growth, dizziness, eyelid edema, hypertension, and nausea have been reported with the prostaglandin analogs in post-marketing experience.

One report suggests that betaxolol administered as the suspension (Betoptic S) reduces the incidence of stinging upon instillation.¹⁶⁸

A study with 30 children (32 eyes; mean age 10.5 years) evaluated the safety and efficacy of brimonidine with a mean follow-up of 10.8 months.¹⁶⁹ Most patients were also on other glaucoma mediations. Two 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. In the 11 eyes with evaluable IOP data, brimonidine 0.2% significantly reduced IOP (mean decrease of 6.7%; $p=0.04$).

In 2 clinical studies in patients with elevated IOP, brinzolamide (Azopt) was associated with less stinging and burning upon instillation than dorzolamide (Trusopt).¹⁷⁰

Somnolence is the most common adverse effect with brimonidine use and is seen in up to 50% to 83% of children ages 2 to 6 years. Decreased alertness has also been reported with brimonidine. In children ages 7 years and older, patients reported somnolence (25%) with brimonidine.

Prolonged use of echothiophate iodide may cause conjunctival thickening and nasolacrimal canal obstruction. Iris cysts, lens opacities, and latent iritis or uveitis may occur.

In a clinical study comparing latanoprost solution (Xalatan) and timolol, adverse effects reported more often with latanoprost solution than with timolol included foreign body sensation (13% versus 8%), punctate keratitis (10% versus 9%), conjunctival hyperemia (8% versus 3%), and increased iris pigmentation (7% versus 0%); stinging was reported more often with timolol (9% versus 12%).¹⁷¹

In a clinical study comparing netarsudil and timolol, adverse effects reported more often with netarsudil than with timolol included conjunctival hyperemia (53% versus 8.2%), conjunctival hemorrhage (13.3% versus 0.5%), erythema of eyelid (5.9% versus 0%), vision blurred (5.4% versus 0.5%), corneal deposits (5.4% versus 0%), visual acuity reduced (3.9% versus 1.4%), conjunctival vascular disorder (3.9% versus 0.5%), eye irritation (3.9% versus 0.5%), conjunctivitis allergic (6% versus 0%), instillation site erythema (11.8% versus 1.9%); instillation site pain occurred more often with timolol (14.8% versus 20.2%)

A small, 12-month randomized study evaluated preservative-free timolol gel and preserved timolol eye drops on conjunctiva and tear parameters in 42 patients with open-angle glaucoma or ocular hypertension.¹⁷² This study reported that, as measured by *in vivo* conjunctival confocal microscopy (IVCM), preservative-free beta-blocker gel induces fewer changes at ocular surface than preserved beta-blockers.

Pediatrics

Brimonidine 0.2% (Alphagan), brimonidine/timolol (Combigan), and dorzolamide/timolol (Cosopt/Cosopt PF) have been studied in well-controlled clinical trials involving children ages 2 years and older.

The safety and effectiveness of brimonidine ophthalmic solution have not been studied in pediatric patients below the age of 2 years. Brimonidine (Alphagan P, Simbrinza) is contraindicated in children less than 2 years of age.

Dorzolamide (Trusopt) has been studied in a well-controlled pediatric clinical trial of 3 months duration.¹⁹⁸ Safety and effectiveness of dorzolamide and timolol (Betimol, Timolol GFS, Timoptic, Timoptic in Ocudose, Timoptic XE) have been established when administered individually in pediatric patients aged 2 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 2 years have not been established for these 2 agents.

Safety and effectiveness of brimonidine/timolol (Combigan) have been established for ages 2 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 2 to 7 years). Brimonidine/timolol is not recommended for use in children less than the age of 2 years.

Safety and IOP-lowering effect of betaxolol (Betoptic S) have been demonstrated in pediatric patients in a 3-month, multicenter, double-masked, active-controlled trial. Age was not specified.

Safety and efficacy of echothiophate iodide (Phospholine Iodide) have been demonstrated in pediatric patients. Age was not specified.

In children under 2 years of age, 1 drop of pilocarpine 1% should be instilled 3 times daily. Children 2 years of age and older should be dosed as adults.

Bimatoprost (Lumigan), latanoprostene bunod (Vyulta), tafluprost (Zioptan), and travoprost (Travatan Z) use in pediatric patients less than the age of 16 years is not recommended because of potential safety concerns related to increased pigmentation following long-term chronic use.

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

Pregnancy

Most agents used in the treatment of ocular hypertension and glaucoma are Pregnancy Category C. Brimonidine (Alphagan P) is Pregnancy Category B classification.

The labeling for apraclonidine (Iopidine), echothiophate iodide (Phospholine Iodide), and timolol (Timoptic, Timoptic in Ocudose) advises that there are no adequate studies in pregnant women; use during pregnancy only if the potential benefits justify the potential risks to the fetus.

The labeling for bimatoprost (Lumigan) states that there are no adequate studies in pregnant women; there is no increased risk of major birth defects or miscarriages reported postmarketing.

There are data for use of latanoprostene bunod (Vyzulta) in pregnant women; however, in animal studies latanoprostene bunod is associated with miscarriages and fetal harm when given intravenously.

Systemic exposure to netarsudil (Rhopressa, Rocklatan) is low. There are no data on use of netarsudil, including the combination product netarsudil/latanoprost, in pregnant women to advise of developmental risks to the fetus.

African Americans

Travoprost (Travatan Z) has been shown to provide additional IOP reduction in the African American population compared to other populations.¹⁹⁹ It is not currently known whether this difference is due to race or to heavily pigmented irides.

Severe Renal or Hepatic Impairment

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 (Iopidine) 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 studied in patients with renal or hepatic impairment. Brinzolamide (Azopt) and dorzolamide (Trusopt) have not been studied in patients with severe renal impairment; however, since their metabolites are primarily renally excreted, neither product is recommended in this population. Brinzolamide/brimonidine (Simbrinza) has not been well studied in patients with severe renal impairment and it not recommended in such patients. Caution should be used when prescribing brinzolamide/brimonidine in patients with hepatic impairment, since it has not been studied in this population.

Drug	Strength	Dosing	Availability
Beta-blockers			
betaxolol	0.5%	1 to 2 drops twice daily	5 mL, 10 mL, 15 mL (generic only)
betaxolol (Betoptic S)	0.25%	1 drop twice daily	10 mL and 15 mL (brand only)
carteolol	1%	1 drop twice daily	5 mL, 10 mL, 15 mL
levobunolol	0.5%	1 to 2 drops once or twice daily	5 mL, 10 mL, 15 mL
timolol solution (Betimol)	0.25% and 0.5%	1 drop twice daily	0.25% – 5 mL 0.5% – 5 mL, 10 mL, 15 mL
timolol solution (Timoptic)	0.25% and 0.5%	1 drop twice daily	0.25% – 5 mL, 10 mL (generic only), 15 mL (generic only) 0.5% – 5 mL, 10 mL, 15 mL (generic only) Ocudose (0.25%, 0.5%): 0.2 mL x 60 blister packs PF
timolol gel forming solution (Timolol GFS)	0.25% and 0.5%	1 drop daily	0.25% – 5 mL 0.5% – 5 mL
timolol gel forming solution (Timoptic XE)	0.25% and 0.5%	1 drop daily	0.25% – 5 mL 0.5% – 5 mL
timolol LA solution (Istalol)	0.5%	1 drop daily	2.5 mL, 5 mL
Carbonic Anhydrase Inhibitors			
brinzolamide (Azopt)	1%	1 drop 3 times daily	10 mL, 15 mL
dorzolamide (Trusopt)	2%	1 drop 3 times daily	1 mL (generic only), 10 mL
Cholinesterase Inhibitors			
echothiophate iodide (Phospholine Iodide)	0.125%	1 drop once daily	6.25 mg package for reconstitution to 5 mL
Miotic, Topical			
pilocarpine	1%, 2%, and 4%	Adults, adolescents, and children ≥ 2 years: 1 drop up to 4 times daily Infants and Children < 2 years: 1 drop of the 1% solution 3 times daily	15 mL

PF = preservative-free

Dosages (continued)

Drug	Strength	Dosing	Availability
Prostaglandins			
bimatoprost (Lumigan)	0.01% and 0.03%	1 drop daily in evening	0.01% – 2.5 mL, 5 mL, 7.5 mL (brand only) 0.03% – 2.5 mL, 5 mL, 7.5 mL (generic only)
latanoprost emulsion (Xelpros)	0.005%	1 drop daily in evening	2.5 mL PF
latanoprost solution (Xalatan)	0.005%	1 drop daily in evening	2.5 mL 2.5 mL x 3 packages
latanoprostene bunod (Vyzulta)	0.024%	1 drop daily in evening	2.5 mL, 5 mL
tafluprost (Zioptan)	0.0015%	1 drop daily in evening	Pouches containing 30 x 0.3 mL single use containers
travoprost (Travatan Z)	0.004%	1 drop daily in evening	2.5 mL, 5 mL
Rho Kinase Inhibitor			
netarsudil mesylate (Rhopressa)	0.02%	1 drop daily in evening	2.5 mL
Sympathomimetics			
apraclonidine (Iopidine)	0.5%	1 to 2 drops 3 times daily	5 mL, 10 mL
apraclonidine (Iopidine)	1%	1 drop 1 hour prior to laser surgery; 1 drop immediately following a laser surgical procedure	0.1 mL unit dose x 24 per carton (brand only)
brimonidine (Alphagan P)	0.1% (brand only) and 0.15%	1 drop 3 times daily	5 mL, 10 mL, 15 mL
brimonidine	0.2%	1 drop 3 times daily	5 mL, 10 mL, 15 mL
Combination Products			
brimonidine/brinzolamide (Simbrinza)	0.2% brimonidine and 1% brinzolamide	1 drop 3 times daily	8 mL
brimonidine/timolol (Combigan)	0.2% brimonidine and 0.5% timolol	1 drop twice daily	5 mL, 10 mL, 15 mL
dorzolamide/timolol (Cosopt, Cosopt PF)	2% dorzolamide and 0.5% timolol	1 drop twice daily	Cosopt: 10 mL Cosopt PF: 0.2 single-dose vials (15 and 60 per carton)
netarsudil/latanoprost (Rocklatan)	0.02% netarsudil and 0.005% latanoprost	1 drop daily in evening	2.5 mL

PF = preservative-free

When administering other ophthalmic drugs, a period of at least 5 minutes should elapse before administering a prostaglandin analog; if brinzolamide is administered with another topical ophthalmic drug, the drugs should be administered at least 10 minutes apart.

Contact lenses should be removed prior to instillation of pilocarpine, select beta-blockers (betaxolol [Betoptic-S], levobunolol, timolol [Betimol, Istalol, Timolol]), apraclonidine (Iopidine), carbonic anhydrase inhibitors (Azopt, Trusopt), prostaglandin analogs (Lumigan, Travatan Z, Vyzulta, Xalatan, Xelpros, Zioptan), rho kinase inhibitors (Rhopressa, Rocklatan), and the combination products (Combigan, Cosopt, Simbrinza). Lenses may be reinserted 5 to 15 minutes after administration,

depending on the product. Timoptic XE and Timolol GFS have not been studied in patients wearing contact lenses. Carteolol should not be used with contact lenses.

Latanoprost emulsion (Xelpros) FDA-approval was under the 505(b)(2) pathway, in which at least some of the safety and efficacy data was from clinical studies not conducted by or for the applicant.

CLINICAL TRIALS

Search Strategy

Articles were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the FDA-approved 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% 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 and/or 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 2 medications for the treatment of glaucoma not commercially available as a combination product in the United States have not been included in this review. No relevant placebo-controlled or comparison studies were available for echothiophate iodide (Phospholine Iodide).

bimatoprost (Lumigan) versus latanoprost solution (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.²²⁵ Baseline IOPs were 22 to 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 60 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%.²²⁶ Patients underwent a washout period and then were randomized to daily bimatoprost 0.03% or latanoprost 0.005% for 3 months. Both active therapies had significant reductions in IOP compared to baseline at all diurnal measurements ($p < 0.001$). The morning (8:00 a.m.) measurement was significantly lower with bimatoprost at 2 follow-up visits ($p \leq 0.033$). After 3 months, the mean IOP reductions from baseline were -2.8 to -3.8 mm Hg (17.5% to 21.6%) with bimatoprost and -2.1 to -2.6 mm Hg (12.7% to 16.2%) for latanoprost. The overall mean reduction in IOP was greater with bimatoprost (-3.4 mm Hg, 19.9%) than latanoprost (-2.3 mm Hg, 14.6%; $p = 0.035$). Adverse effects and clinical success did not differ between the 2 groups.

bimatoprost (Lumigan) versus 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.²²⁷ Each therapy was given once daily for 3 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%) for bimatoprost and -6.2 to -6.9 mm Hg (25% to 28%) for travoprost. By the end of the study, 85% and 68% of patients receiving bimatoprost and travoprost, respectively, achieved at least a 20% mean reduction of IOP. Patients with mean IOP reductions of at least 40% were reported in 31.9% and 20.9% 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 6 months.²²⁸ Five study visits recorded IOP at 3 time points (9:00 a.m., 1:00 p.m., and 4:00 p.m.) and found no significant differences between the 2 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 9:00 a.m., when mean IOP reduction was 7.1 mm Hg (27.9%) for bimatoprost and 5.7 mm Hg (23.3%) with travoprost ($p = 0.014$). Ocular redness was the most common adverse effect.

A prospective, investigator-masked, multicenter clinical trial enrolled adult patients ($n = 266$) who were diagnosed with glaucoma or ocular hypertension and inadequate IOP control after at least 30 days on latanoprost 0.005% solution monotherapy.²²⁹ Mean diurnal IOP on latanoprost was approximately 19 mm Hg at baseline in both treatment groups. After a 2 week run-in period on latanoprost, patients were randomized to bimatoprost 0.03% or travoprost 0.004%. A larger percentage of patients in the travoprost group were male (51% versus 38%). The primary efficacy outcome measures were mean IOP at each time point and mean diurnal IOP. After replacement of latanoprost therapy with bimatoprost or travoprost therapy, the mean IOP was significantly lower with bimatoprost than with travoprost at the 09:00 time point at month-1 and the 16:00 time point at month-3 ($p < 0.005$). The mean diurnal IOP was significantly lower with bimatoprost than with travoprost at both months 1 and 3 ($p < 0.005$). A mean reduction from baseline diurnal IOP of 1.2 mm Hg (95% confidence interval [CI], 0.8 to 1.6) at month-1 and 1.4 mm Hg (95% CI, 0.9 to 1.8) at month-3, was reported in the travoprost group, while mean decreases from baseline diurnal IOP of 1.9 mm Hg (95% CI, 1.6 to 2.3) at month-1 and 2.1 mm Hg (95% CI, 1.7 to 2.5) at month-3 were reported for bimatoprost. Both bimatoprost and travoprost were well tolerated and associated with a low incidence of adverse events.

bimatoprost (Lumigan) versus timolol (Timoptic)

In 2 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%.²³⁰ Primary outcome measure was diurnal IOP, measured at 8:00 a.m., 10:00 a.m., and 4:00 p.m. Bimatoprost once daily provided significantly lower mean IOP than timolol at 8:00 a.m., 10:00 a.m., and 4:00 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 10:00 a.m. during month 12, the mean reduction in IOP from baseline was 30% with bimatoprost and 21% with timolol ($p < 0.001$). A significantly higher percentage of patients receiving bimatoprost daily (58%) than timolol (37%) achieved IOP at or below 17 mm Hg

($p < 0.001$). The most common adverse effect with bimatoprost was hyperemia. Study authors concluded that once-daily administration of bimatoprost provides sustained IOP lowering that was favored over bimatoprost twice daily or timolol.

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.²³¹ Scheduled visits were conducted pre-study, baseline, weeks 2 and 6, and month 3. At month 3, the mean reduction in IOP from baseline was 35.2% with bimatoprost once daily, 30.4% with bimatoprost twice daily, and 26.2% 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) versus dorzolamide/timolol (Cosopt)

In a multicenter, double-blind study, 177 patients with glaucoma or ocular hypertension who were not controlled after at least 2 weeks of timolol maleate 0.5% were randomized to bimatoprost 0.03% once daily or combined dorzolamide 2%/timolol 0.5% twice daily for 3 months.²³² Bimatoprost provided significantly greater IOP-lowering effects and better diurnal control than dorzolamide/timolol. At 8:00 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 8:00 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.²³³ 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 2 products.

brimonidine 0.15% (Alphagan P) versus brimonidine 0.2%

In a 3-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.²³⁴ All patients were taking brimonidine 0.2% twice daily for at least 6 weeks prior to study entry and had IOP ≤ 21 mm Hg. Patients were then randomized to brimonidine 0.15% or 0.2% for 3 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 3 times daily was found to be equally efficacious to brimonidine 0.2% three times daily in the reduction of IOP.²³⁵ Diurnal IOP was measured at 4 time points between 8:00 a.m. and 5:00 p.m. at baseline, week 6, and at months 3, 6, 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% 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% versus 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.²³⁶ Patients were randomized to brimonidine or betaxolol twice daily for 4 weeks. Mean IOP reductions after 4 weeks were -5.96 mm Hg with brimonidine and -5.07 mm Hg with betaxolol (p=NS). More brimonidine (64.2%) patients achieved a reduction of greater than 20% in IOP than betaxolol patients (47.4%; p=0.033). More patients treated with betaxolol reported hyperemia (p=0.011).

brimonidine 0.2%/brinzolamide 1% (Simbrinza) versus brimonidine 0.2% (Alphagan) or brinzolamide 1% (Azopt)

Data were pooled from 2 phase 3 studies comparing brinzolamide 1%/brimonidine 0.2% fixed combination with its individual components, each administered 3 times a day.²³⁷ The studies included a total of 1,350 patients with open-angle glaucoma or ocular hypertension. The primary outcome measurement was intraocular pressure (IOP) at month 3 measured at 8:00 a.m., 10:00 a.m., 3:00 p.m., and 5:00 p.m. Baseline IOP levels were similar among all groups. At 3 months, mean IOP of the fixed combination group was significantly lower than that of either monotherapy group (p<0.0001) at all 4 time points. The proportion of patients that experienced at least 1 adverse event, which were mostly ocular in nature, were 24.6% for fixed-combination therapy, 18.7% for brinzolamide, and 17.4% for brimonidine. One serious adverse effect, moderate intensity chest pain, considered related to brinzolamide therapy resulted in study discontinuation.

In a randomized, double-masked, multicenter, 3-month, study with a 3-month safety extension, patients (n=690) with open-angle glaucoma or ocular hypertension were randomized 1:1:1 to brinzolamide 1%/brimonidine 0.2% fixed combination or its individual components, each administered 3 times a day.²³⁸ At 3 months, the IOP in patients treated with combination therapy was significantly lower than that of either monotherapy group. IOP at 6 months was similar to those at 3 months. Thirty-three percent of patients on combination therapy experienced at least 1 treatment-related adverse event compared to 18.8% for brinzolamide and 24.7% for brimonidine. Seven patients in each group experienced serious adverse reactions. Seventy-seven patients discontinued therapy due to treatment-related adverse events (combination therapy 17.2%; brinzolamide, 2.1%; brimonidine, 14.5%). No new or increased risks were identified with use of combination therapy as compared to either monotherapy.

In a 6-month, phase 3, double-masked trial, 560 patients with primary open-angle glaucoma or ocular hypertension who had inadequate IOP reduction with their current drug regimen were randomized to a fixed combination of brinzolamide 1%/brimonidine 0.2% or monotherapy with either brinzolamide 1% or brimonidine 0.2%; all therapies were dosed twice daily.²³⁹ The primary endpoint was mean change in diurnal IOP from baseline to month 3. At month 3, combination therapy lowered diurnal IOP

to a significantly greater extent than brinzolamide (mean difference, -1.4 mm Hg; $p < 0.0001$) and brimonidine (-1.5 mm Hg; $p < 0.0001$). Results at month 6 were consistent with those taken at month 3. The safety profile was consistent for all 3 groups; however, incidence of hyperemia of the eye was slightly lower with brinzolamide than with brimonidine or combination therapy.

brimonidine/timolol (Combigan) versus timolol (Timoptic) or brimonidine

In 2 identical, randomized, 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 12 months to evaluate IOP-lowering efficacy and safety of the 3 products.²⁴⁰ 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 8:00 a.m., 10:00 a.m., and 3:00 p.m. ($p < 0.001$), but not at 5:00 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% with brimonidine/timolol, 30.6% with brimonidine, and 5.1% with timolol.

brimonidine/timolol (Combigan) versus dorzolamide/timolol (Cosopt)

The combinations of brimonidine/timolol and dorzolamide/timolol were compared in a prospective, randomized, double-blind, crossover study with 25 patients with primary open-angle glaucoma in a short-term, small population study.²⁴¹ After 6 weeks of timolol 0.5% twice daily treatment, patients were randomized to fixed combinations of timolol with either brimonidine or dorzolamide given twice daily for 6 weeks. Subsequently, patients were then crossed over to receive 6 weeks of the alternate therapy. At all visits, IOP was measured at 9:00 a.m., noon, and 4:00 p.m. Of the 20 patients who completed the study, the mean diurnal IOP was 20.28 mm Hg at the timolol-treated baseline. The mean diurnal IOP was 16.28 mm Hg for brimonidine combination and 17.23 mm Hg for the dorzolamide combination (difference: 0.95 mm Hg; 95% CI, 0.1 to 1.8; $p = 0.03$). At the specific time points, the mean IOP at 9:00 a.m. (pre-dosing) was 20.95 mm Hg at baseline. Brimonidine/timolol combination reduced the 9:00 a.m. mean IOP to 15.85 mm Hg and the dorzolamide/timolol combination reduced mean IOP at the same time point to 17.55 mm Hg (difference: 1.7; 95% CI, 0.8 to 2.6; $p = 0.001$). For the IOP measurements at noon and 4:00 p.m., the mean changes from baseline were comparable. Patients achieving at target of IOP < 18 mm Hg were comparable between the 2 groups ($p = \text{NS}$). No treatment-related adverse effects were reported in either group.

brinzolamide (Azopt) versus dorzolamide (Trusopt)

In a randomized, placebo-controlled, double-blind study, brinzolamide and dorzolamide were compared for efficacy, safety, and tolerability.²⁴² Patients were randomized to brinzolamide 1% two or three times daily, dorzolamide 2% three times daily, or placebo given 3 times daily. A total of 463 patients were randomized with available data for 409 patients for efficacy comparisons. Mean IOP changes after 3 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 3 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%) compared to brinzolamide (3%). Two other studies have confirmed less

discomfort with brinzolamide upon dose instillation compared to dorzolamide; however, pain may reduce over time with dorzolamide use.^{243,244}

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

Investigators evaluated the use of the combination product versus the individual components in a 2-part study. A total of 131 patients were randomized to dorzolamide/timolol or a topical carbonic anhydrase inhibitor and non-selective beta-blocker.²⁴⁵ Patients underwent a 1-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 1 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 that, 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 1 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% of eyes had IOP readings equal to or lower than the baseline readings.

latanoprost solution (Xalatan) versus brimonidine

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 3 months.²⁴⁶ The prospective, multicenter, double-blind trial randomized 115 patients with mean baseline IOP of 21.3 mm Hg while on beta-blocker therapy. After 1 month of therapy, if at least 15% reduction in IOP at peak effect was not achieved, patients switched to the alternative therapy. Response rates (at least 15% reduction in IOP) and IOP reduction were similar between brimonidine and latanoprost at 1 month (4.88 mm Hg [22.8%] with brimonidine and 5.01 mm Hg [23.5%] with latanoprost; $p = 0.798$). Of the patients with successful IOP reduction at 1 month, and continued on the initial study medication, the 3-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% additional reduction in IOP for 3 months (28 of 38 patients on brimonidine versus 30 of 36 patients on latanoprost achieved at least a 15% IOP reduction at month 3; $p = 0.314$). 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, 3-month, multicenter, double-blind trial.²⁴⁷ The primary outcome measure was response rate, defined as the percentage of patients achieving at least 20% reduction in IOP from baseline to month 3. 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% of the latanoprost group achieved at least 20% reduction in IOP compared to baseline. The mean IOP reduction from baseline in each group at month 3 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% decrease in IOP versus latanoprost (88% versus 59%; $p = 0.01$). The previously treated patients

achieved at least 20% reduction in IOP more frequently with latanoprost than brimonidine, although the difference was not significant (88% versus 74%; p=NS).

latanoprost solution (Xalatan) versus dorzolamide/timolol (Cosopt)

Two 3-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.²⁴⁸ 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 8:00 a.m., 10:00 a.m., 2:00 p.m., and 4:00 p.m. After 3 months, mean daytime diurnal IOP was similar for both groups; 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% reduction in IOP (target level) in 15% of the dorzolamide/timolol and 13% of the latanoprost groups.²⁴⁹ 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).

latanoprostene bunod (Vyzulta) versus timolol

LUNAR:²⁵⁰ A phase 3, randomized, double-masked, parallel-group, noninferiority study assessed the efficacy and safety of latanoprostene bunod compared to timolol in 420 adults with open angle glaucoma or ocular hypertension. Participants were randomized 2:1 to latanoprostene bunod 0.024% once daily or timolol 0.5% twice daily. The primary endpoint was the mean IOP at 9 different time points (8 AM, 12 PM, and 4 PM at week 2, week 6, and month 3) with a noninferiority margin set at ≤ 1 mm Hg in the upper limit of the 95% CI. Latanoprostene bunod was found to be noninferior to timolol at all time points. In addition, it led to statistically significantly greater reductions in IOP at most efficacy time points (excluding the 8 AM time point at week 2). A mean IOP < 18 mm Hg occurring at all 9 efficacy assessment time points occurred in 17.1% of patients assigned latanoprostene bunod compared to 11.1% assigned timolol. At least 1 ocular adverse effect occurred in 23.8% of those in the latanoprostene bunod treatment group compared to 13.3% of those in the timolol treatment group. Much of these differences were due to a higher rate of conjunctival hyperemia, eye irritation, and eye pain in the latanoprostene bunod group.

APOLLO:²⁵¹ A phase 3, randomized, double-masked, parallel-group study, assessed the efficacy and safety of latanoprostene bunod compared to timolol in 420 adults with open angle glaucoma or ocular hypertension. Participants were randomized 2:1 to latanoprostene bunod 0.024% once daily or timolol 0.5% twice daily, and the primary endpoint was the mean IOP at 9 different time points (8 AM, 12 PM, and 4 PM at week 2, week 6, and month 3). Latanoprostene bunod led to statistically significantly greater reductions in IOP at all efficacy 9 time points ($p \leq 0.002$ for all time points). Following the 3-month efficacy phase, APOLLO also included a 9-month open-label safety phase. Adverse effects were found to be similar between treatment groups.

netarsudil mesylate (Rhopressa) versus timolol

ROCKET-1 (Study 301; n=756) was a double-masked, multicenter, noninferiority study comparing ophthalmic netarsudil to timolol in patients with open-angle glaucoma or ocular hypertension.^{252,253} Patients were randomized (1:1) to netarsudil 0.02% administered once daily or timolol 0.5%

administered twice daily. Study duration was 3 months. After 3 months, both treatment groups had statistically significant mean reductions in IOP compared to baseline ($p < 0.001$). From baseline to day 90 at 16:00 in those with a baseline IOP of < 25 mm Hg, the IOP decreased by 3.6 mm Hg and 3.2 mm Hg in the netarsudil and timolol groups, respectively (treatment difference: 0.4 mm Hg; 95% CI, -1 to 0.3). Patients with an IOP or ≥ 25 mm Hg to < 27 mm Hg at baseline demonstrated a reduction in IOP of 2.6 mm Hg and 4.9 mm Hg in the netarsudil and timolol groups, respectively (treatment difference: 2.3 mm Hg; 95% CI, 1.2 to 3.5). Non-inferiority was met, as the difference between groups did not exceed an upper 95% CI of < 1.5 mm Hg at all time points and < 1 mm Hg at most.

ROCKET-2 (Study 302; $n=411$) was a double-masked, multicenter, noninferiority study comparing ophthalmic netarsudil to timolol in patients with open-angle glaucoma or ocular hypertension.^{254,255} Patients were randomized (1:1) to netarsudil 0.02% administered once or twice daily or timolol 0.5% twice daily, respectively. Study duration was 12 months. From baseline to day 90 at 16:00 in patients with a baseline IOP of < 25 mm Hg, the IOP decreased by 3.4 mm Hg and 3.7 mm Hg in the netarsudil and timolol groups, respectively (treatment difference: 0.3 mm Hg; 95% CI, -0.4 to 1). Patients with a baseline of IOP ≥ 25 mm Hg to < 27 mm Hg had a reduction in IOP of 4.4 mm Hg and 4.3 mm Hg in the netarsudil and timolol groups, respectively (treatment difference 0.1 mm Hg; 95% CI, -1.2 to 1). Non-inferiority was defined the same as ROCKET-1 and was met.

Rocket-4 (Study 304; $n=623$), a blinded, noninferiority study compared ophthalmic netarsudil 0.02% administered once daily to timolol 0.5% administered twice daily over 6 months in patients with open-angle glaucoma or ocular hypertension.²⁵⁶ The baseline IOP in patients was < 30 mm Hg. From baseline to day 90 at 16:00, patients with an IOP of < 25 mm Hg had a decrease of 3.9 mm Hg in both the netarsudil and timolol groups, respectively (treatment difference, 0 mm Hg; 95% CI, -0.6 to 0.5). Patients with an IOP of ≥ 25 mm Hg to < 30 mm Hg demonstrated a reduction in IOP at day 90 at 16:00 of 3.9 mm Hg and 5 mm Hg in both the netarsudil and timolol groups, respectively (treatment difference, 1.1 mm Hg; 95% CI, 0.2 to 1.9). Non-inferiority netarsudil to timolol at the target IOPs was demonstrated.

netarsudil/latanoprost (Rocklatan) versus netarsudil (Rhopressa) versus latanoprost

The MERCURY 1 (12 month trial) and MERCURY 2 (3 month trial) randomized trials compared the efficacy and safety of netarsudil/latanoprost 0.02%/0.005% with solution to the individual components netarsudil 0.02% and latanoprost 0.005% in patients with open-angle glaucoma and ocular hypertension with IOP < 36 mmHg.²⁵⁷ In each arm, the studied product was administered as 1 drop in both eyes daily in the evening. The average IOP lowering effect of the combination product was 1 to 3 mmHg greater than monotherapy with either netarsudil 0.02% or latanoprost 0.005% throughout 3 months. In MERCURY 2, IOP reductions were maintained throughout 12 months.

tafluprost (Zioptan) with preservative versus latanoprost solution with preservative (Xalatan)

In a double-masked, active-controlled, parallel-group, phase 3 study 533 patients with open-angle glaucoma or ocular hypertension were randomized to receive tafluprost 0.0015% or latanoprost 0.005%, both containing benzalkonium chloride as preservative.²⁵⁸ The primary efficacy outcome measure was the change from baseline in the overall diurnal IOP based on measurements taken at 8:00 a.m., noon, 4:00 p.m., and 10:00 p.m. At baseline, the mean IOP in the worse eye was somewhat higher in the tafluprost group than in the latanoprost group, with a mean diurnal IOP of 24.3 ± 3 mm Hg and 23.8 ± 2.8 mm Hg, respectively. Both treatments had a significant IOP-lowering effect measured

at week 2 which persisted throughout the study, (-7.1 mm Hg for tafluprost and -7.7 mm Hg for latanoprost at 24 months). Although the IOP-lowering effect during the study was larger with latanoprost, this difference was clinically small and the noninferiority of tafluprost to latanoprost over all diurnal IOP measurements was shown with ANOVA and almost reached with ANCOVA (upper limits of the 95% CI 1.38 and 1.52 for the overall period, respectively). The noninferiority limit was 1.5 mm Hg. Ocular adverse events were reported by 48.1% of patients in the tafluprost group compared with 44.3% of patients in the latanoprost group. The ocular adverse events were comparable in terms of type and severity.

tafluprost preservative-free (Zioptan) versus timolol preservative-free (Timoptic PF)

In a double-blind, parallel-group, active-control trial, after completing a washout period of existing ocular hypotensive treatment, 643 patients with IOP ≥ 23 and ≤ 36 mm Hg in at least 1 eye were randomized to 1 drop of tafluprost preservative-free (PF) 0.0015% instilled in affected eye every evening or 1 drop of timolol PF 0.5% instilled twice daily for 12 weeks.²⁵⁹ Baseline IOPs were similar between the 2 groups. IOPs assessed during the 12-week visit ranged from 17.4 to 18.6 mm Hg for tafluprost PF and 17.9 to 18.5 mm Hg for PF timolol. Similar percentages of tafluprost PF and timolol PF patients reported ocular pain/stinging/irritation (4.4% versus 4.6%) and pruritus (2.5% versus 1.5%). Conjunctival hyperemia was reported in 4.4% of patients on tafluprost PF versus 1.2% of patients on timolol PF ($p=0.016$). Tafluprost PF was shown to be non-inferior to timolol PF.

timolol (Timoptic) versus timolol LA (Istalol)

Timolol LA contains potassium sorbate, which enhances the ocular bioavailability of timolol and reduces administration frequency to once daily.²⁶⁰ The 2 formulations were compared to evaluate efficacy and safety in 332 patients with open-angle glaucoma or ocular hypertension.²⁶¹ In the multicenter, prospective, double-masked, parallel-group trial, patients were randomized to timolol LA 0.5% once daily or timolol 0.05% twice daily for 1 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 2 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%) at peak effect and 5 to 6 mm Hg (20.8% to 24.7%) at trough. Burning and stinging on instillation, which was mostly described as mild, was reported by 41.6% in the timolol LA group and 22.9% with timolol ($p=0.001$). No patients withdrew due to instillation adverse effects. Discontinuation rates were 6% and 4.2% for timolol LA and timolol, respectively.

timolol ER gel forming solution (Timoptic GFS) versus timolol (Timoptic)

In controlled, double-masked, multicenter clinical studies, timolol ER administered once daily was compared to timolol maleate ophthalmic solution administered twice daily in equivalent concentrations.²⁶² Timolol ER demonstrated similar effectiveness in lowering IOP as timolol in lowering IOP. Repeated observations over a 3-month study period indicate that the IOP-lowering effect of Timolol ER was consistent. The safety profile was similar between the 2 products.

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

Efficacy and safety of timolol 0.5% or brinzolamide 1%, when given in combination with travoprost 0.004%, were compared in 192 patients with ocular hypertension or primary open-angle glaucoma.²⁶³ In the double-blind, randomized study, patients were started on travoprost every evening for 4 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% of brinzolamide-treated patients and 6% with timolol-treated patients (p=0.06).

travoprost (Travatan) versus timolol (Timoptic)

Two double-blind, randomized studies, one 6-month (n=605) and one 9-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.^{264,265} Enrollment required baseline IOP between 24 and 36 mm Hg in at least 1 eye. Travoprost 0.0015% and 0.004% significantly lowered mean IOP measurements more than timolol in both studies. In the 9-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 6-month study, 29.2% of travoprost 0.0015% patients experienced hyperemia compared to 42.8% of travoprost 0.004% and 8.9% of timolol patients. In the 9-month study, timolol was better tolerated than either strength of travoprost.

travoprost (Travatan) versus travoprost (Travatan) plus 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.²⁶⁶ Patients were followed for 6 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.

travoprost (Travatan) versus latanoprost solution (Xalatan), versus 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.²⁶⁷ 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% or greater IOP reduction from diurnal baseline or IOP 17 mm Hg or less, were 49.3% and 54.7% for travoprost 0.0015% and 0.004%, respectively, compared with 49.6% for latanoprost and 39% for timolol. Iris pigmentation change was observed in 5% of patients receiving travoprost 0.0015%, 3.1% of patients receiving travoprost 0.004%, 5.2% of patients receiving latanoprost, and none of the patients receiving timolol.

In 2 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.²⁶⁸ 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 African Americans treated with travoprost, and travoprost was

superior to latanoprost in African Americans. Timolol lowered the mean IOP to a greater extent in non-African Americans patients.

travoprost (Travatan) versus latanoprost solution (Xalatan) versus 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.²⁶⁹ The study was a multicenter, double-blind, randomized clinical trial based in the U.S. Baseline IOP after washout was at least 23 mm Hg in 1 or both eyes. Patients were randomized to one of the 3 therapies and followed for reduction in IOP and hyperemia. After 12 weeks, IOP was measured at 8:00 a.m., 12:00 p.m., 4:00 p.m., and 8:00 p.m. IOP readings were similar at all time points for all drugs (16 to 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.²⁷⁰ Patients were treated with each agent for 1 month, each given in a random sequence with a 30-day washout period between drugs. IOP was recorded at 8 time points in a 24-hour period at baseline and following treatment with each agent. All 3 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.

META-ANALYSES

A meta-analysis evaluated 9 studies of the prostaglandin analogs for the management of glaucoma or ocular hypertension.²⁷¹ A total of 1,318 patients were evaluated in the analysis. Patients treated with travoprost or bimatoprost had lower IOP levels at the end of follow-up (-0.98 mm Hg [95% CI, -2.08 to 0.13; $p=0.08$] and -1.04 mm Hg [95% CI, -2.11 to 0.04; $p=0.06$], respectively) than those treated with latanoprost solution. 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.²⁷²

Another systematic review evaluated the IOP lowering efficacy and tolerability of the prostaglandin analogs in 8 trials with 1,610 patients with ocular hypertension or primary open-angle glaucoma.²⁷³ The main efficacy outcome measures were IOP measurements taken at 8:00 a.m., noon, 4:00 p.m., and 8:00 p.m., the change at 3 months from baseline, and tolerability. IOP change from baseline was statistically significantly greatest with bimatoprost, compared with latanoprost solution at all time points (8:00 a.m. $p = 0.05$, noon $p < 0.001$, 4:00 p.m. $p=0.003$, and 8:00 p.m. $p=0.004$) and with travoprost during the daytime (8:00 a.m. $p = 0.004$, noon $p = 0.02$). Latanoprost and travoprost were comparable in their ability to reduce IOP at all time points ($p \leq 0.82$). Tolerability assessed by the incidence of conjunctival hyperemia. The incidence of hyperemia was less with latanoprost and travoprost (latanoprost versus bimatoprost: relative risk [RR], 0.59; $p<0.001$; 95% CI, 0.5 to 0.69; travoprost versus bimatoprost: RR, 0.84; $p=0.05$; 95% CI, 0.7 to 1).

A meta-analysis evaluated the IOP reduction of several agents in this class.²⁷⁴ 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% of patients had primary open-angle glaucoma or ocular hypertension. The greatest IOP reductions

were reported with timolol, latanoprost solution, travoprost, and bimatoprost, with peak reductions of 27% to 33% and trough reductions of 26% to 29% from baseline.

A meta-analysis of 13 trials (n=1,302) evaluated the efficacy and tolerability of bimatoprost and latanoprost solution.²⁷⁵ Bimatoprost was associated with greater reductions in IOP in the morning compared to latanoprost at 1, 3, and 6 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 3 prostaglandin analogs.²⁷⁶ The combined results showed that latanoprost produced lower occurrence of conjunctival hyperemia than both travoprost (odds ratio [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).

A meta-analysis with 114 randomized controlled-trials (n=20,275) included placebo-controlled and comparator trials published between 1983 and 2013.²⁷⁷ Of the 17 bimatoprost trials in the meta-analysis, 15 evaluated bimatoprost 0.03% and 2 evaluated bimatoprost 0.01%; however, the mean difference in IOP between the 2 strengths is not statistically significant (1.04 [95% CI -0.30 to 2.39]). Mean IOP reduction, measured as mm Hg (95% confidence interval), after at 3 months of treatment are as follows: bimatoprost 5.61 (4.94; 6.29), latanoprost solution 4.85 (4.24; 5.46), travoprost 4.83 (4.12; 5.54), levobunolol 4.51 (3.85; 5.24), tafluprost 4.37 (2.94; 5.83), timolol 3.70 (3.16; 4.24), brimonidine 3.59 (2.89; 4.29), carteolol 3.44 (2.42; 4.46), levobetaxolol 2.56 (1.52; 3.62), apraclonidine 2.52 (0.94; 4.11), dorzolamide 2.49 (1.85; 3.13), brinzolamide 2.42 (1.62; 3.23), and betaxolol 2.24 (1.59; 2.88).

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 intraocular pressure. The American Academy of Ophthalmology states that prostaglandin analogs and beta-blockers are the most frequently used initial therapy for the treatment of open-angle glaucoma. The 2015 guidelines state that prostaglandin analogs are the most effective drugs at lowering intraocular pressure and can be considered as initial medical therapy. Consideration for selecting therapy for the treatment of glaucoma should include cost, adverse effects, intolerance, or adherence. An initial target pressure is at least 20% to 25% lower than pretreatment intraocular pressure, assuming that the measured pretreatment pressure range contributed to optic nerve damage. However, target pressure is an estimate and the adequacy of the target pressure should be periodically reassessed by comparing optic nerve status with prior examinations. 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 intraocular pressure by 15% to 25%. 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 (Timolol GFS, Timoptic, Timoptic XE).

Prostaglandin analogs may be the most effective drugs, achieving up to 33% reductions in intraocular pressure. Many head-to-head comparative studies are performed in small patient populations. The prostaglandin analog tafluprost (Zioptan) is approved for the reduction of intraocular pressure in

patients with open-angle glaucoma or ocular hypertension. It is currently the only preservative-free prostaglandin analog and is available in single use containers. Tafluprost was shown to be non-inferior to latanoprost solution in clinical trials.

Bimatoprost (Lumigan), latanoprost solution (Xalatan), latanoprostene bunod (Vyzulta), and travoprost (Travatan Z) have been shown to have better efficacy compared to timolol. In clinical trials, tafluprost was shown to cause a similar reduction in mean intraocular pressure comparable to timolol. **There are no published studies comparing latanoprost emulsion (Xelpros) 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.

The rho kinase inhibitor, netarsudil (Rhopressa) that is administered once daily, offers a new mechanism for the treatment of ocular hypertension and glaucoma. In clinical trials, monotherapy with netarsudil was shown to be noninferior to timolol. The fixed-dose combination netarsudil/latanoprost (Rocklatan), also administered once daily, demonstrated greater efficacy in IOP lowering than either component alone.

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 intraocular pressure-reducing medications.

The cholinesterase inhibitor, echothiophate iodide (Phospholine Iodide) is indicated for the treatment of glaucoma; however, is not included in the current practice guidelines.

The fixed combination products contain carbonic anhydrase inhibitors and include brimonidine/brinzolamide (Simbrinza), brimonidine/timolol (Combigan), and dorzolamide/timolol (Cosopt, Cosopt PF).

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