Therapeutic Class Overview
Ophthalmic Prostaglandin Analogs

INTRODUCTION

- Glaucoma is an optic neuropathy that causes gradual degeneration of the cells making up the optic nerve. It is the leading cause of blindness and second leading cause of vision loss in the world *(Prum et al 2016)*. Open-angle glaucoma is the most common form; other forms include angle-closure, congenital, and secondary glaucoma *(Jacobs 2017[a], National Eye Institute Web site)*. Patients with open-angle glaucoma initially experience peripheral visual field loss, followed by central field loss, which may progress to irreversible blindness if untreated *(Jacobs 2018)*. The exact etiology of open-angle glaucoma is unknown *(Jacobs 2018)*. Major risk factors for developing open-angle glaucoma include advanced age, African or Hispanic/Latino descent, elevated intraocular pressure (IOP), family history of glaucoma, low ocular perfusion pressure, type 2 diabetes mellitus, and myopia *(Ellis et al 2000, Girkin et al 2004, Lesk et al 2007, Prum et al 2016)*.
- Elevated IOP is the one major risk factor for glaucoma that is treatable. Available evidence suggests that lowering IOP inhibits or reduces the progression of optic nerve damage *(Jacobs 2018)*. Treatment may be initiated in patients with a raised IOP despite having no visual field loss or optic nerve damage. An IOP > 22 mm Hg is generally considered to be elevated and would be treated by most clinicians; however, this number varies according to screening methods, risk factors, and disease progression. The target IOP should be individualized based on response to therapy and disease progression in order to maintain IOP within a range that is unlikely to adversely affect patients' health-related quality of life. The American Academy of Ophthalmology (AAO) recommends an initial target IOP reduction of 25% from pretreated baseline IOP. However, depending on the severity of disease, this target may vary since there is no consensus target IOP below which further visual loss and optic nerve damage will be prevented *(Prum et al 2016)*.
- The current treatment of glaucoma focuses on decreasing IOP by 1 of 3 methods: laser therapy, surgery, or medical intervention *(Prum et al 2016)*. Medical intervention is generally used as initial therapy prior to laser or surgical treatment *(Jacobs 2018)*. Medical intervention includes 5 classes of ophthalmic drugs used for the long-term management of glaucoma: alpha-$_2$ adrenergic agonists, beta adrenergic antagonists, carbonic anhydrase inhibitors, miotics or parasympathomimetics, and prostaglandin analogues *(Jacobs 2018, Micromedex 2018)*. These treatments reduce IOP by either decreasing the amount of aqueous humor produced by the ciliary body or by increasing uveoscleral outflow *(Micromedex 2018, Prum et al 2016)*. Miotics and prostaglandin analogues increase aqueous outflow, while beta adrenergic antagonists and carbonic anhydrase inhibitors decrease aqueous humor production *(Micromedex 2018)*. Alpha-$_2$ adrenergic agonists decrease the amount of aqueous humor formed and increase its outflow *(Micromedex 2018, Prum et al 2016)*.
- Guidelines published in 2010 by the American Optometric Association (AOA) do not recommend preferential use of any drug class, although current guidelines by the AAO generally recommend ophthalmic prostaglandin analogues as first-line pharmacologic therapy in patients with elevated IOP *(AOA 2010, Prum et al 2016)*. Combination or monotherapy with agents from an alternative pharmacologic class is recommended for patients that experience intolerable adverse events or who do not achieve the optimal IOP reduction with first-line agents *(Jacobs 2018)*.
- This class review consists of the ophthalmic prostaglandin analogs, which include Lumigan (bimatoprost), Travatan Z (travoprost), Vyzulta (latanoprostene bunod), Xalatan (latanoprost), and Zioptan (tafluprost). The drugs in this review are approved by the Food and Drug Administration (FDA) to reduce IOP in patients with open-angle glaucoma or ocular hypertension. Sucampo Pharma discontinued Rescula (unoprostone isopropyl solution/drops) in 2015; the discontinuation was not due to safety or efficacy concerns *(Drugs@FDA 2018)*. The branded product Latisse (bimatoprost 0.03%) has not been FDA-approved for IOP-reduction indications. Latisse is indicated to treat hypotrichosis of the eyelashes and will be discussed in this review in an abbreviated manner.
- Medispan Class: Prostaglandins – Ophthalmic

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Latisse (bimatoprost ophthalmic solution) 0.03%	✔

Drug	Generic Availability
Lumigan (bimatoprost ophthalmic solution) 0.01%¶	-
Travatan Z (travoprost ophthalmic solution) 0.004%†	-
Vyzulta (latanoprostene bunod ophthalmic solution) 0.024%	-
Xalatan (latanoprost ophthalmic solution) 0.005%	✔
Zioptan (tafluprost ophthalmic solution) 0.0015%	-
bimatoprost ophthalmic solution, 0.03%	✔

¶ Allergan discontinued brand Lumigan (bimatoprost) 0.03% in 2012; the discontinuation was not due to safety concerns. Generic bimatoprost 0.03% is available, but generic 0.01% is not.

†The original benzalkonium chloride-containing travoprost formulation (brand name: Travatan) was approved by the FDA on March 16, 2001; however, Travatan was discontinued by Alcon in June 2010. In March 2013, travoprost with benzalkonium chloride by Par Pharmaceuticals was approved by an abbreviated new drug application (ANDA); however, this generic product was discontinued on September 7, 2016 *(Clinical Pharmacology 2018)*. Only the brand product, Travatan Z, remains available.

(*Drugs@FDA 2018, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2018*)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	Latisse (bimatoprost)	Lumigan (bimatoprost)†	Travatan Z (travoprost)	Xalatan (latanoprost)	Vyzulta (latanoprostene bunod)	Zioptan (tafluprost)
Reduction of elevated IOP in patients with open-angle glaucoma or ocular hypertension	-	✔	✔	✔	✔	✔
Hypotrichosis of the eyelashes by increasing their growth including length, thickness, and darkness	✔	-	-	-	-	-

† Generic bimatoprost 0.03% shares the same indication as brand Lumigan.

(Prescribing information: bimatoprost ophthalmic solution 0.03% 2017, Latisse 2017, Lumigan 2017, Travatan Z 2017, Xalatan 2017, Vyzulta 2017, Zioptan 2014)

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

- Several comparative trials with the prostaglandin analogs have been published. Ophthalmic bimatoprost appears to have the greatest efficacy in reducing IOP; however, trials have not consistently demonstrated a difference in IOP reduction between travoprost and latanoprost *(Aptel et al 2008, Cantor et al 2006, Cheng et al 2008, Cheng et al 2009[a,b], Denis et al 2007, Li et al 2006, Parrish et al 2003, Sawada et al 2012, van der Valk et al 2009)*.
- A 2016 systematic review and network meta-analysis pooled results from 114 randomized controlled trials that compared a single topical treatment for glaucoma with placebo or active comparator *(Li et al 2016)*. The analysis reported the mean reductions (from greatest to least) in IOP at 3 months were achieved with bimatoprost, latanoprost, travoprost, and tafluprost. The authors concluded all first-line drugs, including prostaglandins, are effective compared to placebo, and that differences between drugs were small and may not be clinically significant. Another systematic review of 32 randomized controlled trials compared prostaglandin analogs for primary open-angle glaucoma, using the β-adrenergic antagonist timolol as a reference comparator. The analysis found that bimatoprost was most likely to achieve treatment success, defined as a 30% reduction in IOP (relative risk [RR], 1.59; 95% confidence interval [CI]: 1.28 to

1.98). The RR for treatment success with latanoprost was 1.32 (95% CI: 1.00 to 1.74), for travoprost was 1.33 (95% CI: 1.03 to 1.72), and for tafluprost was 1.1 (95% CI: 0.85 to 1.42). In terms of tolerability, bimatoprost was associated with the highest risk of developing hyperemia, while latanoprost had the lowest risk *(Lin et al 2014)*.

- A pooled analysis of 2 similarly designed, Phase 3, double-masked, active control (AC), multi-center (MC), noninferiority trials (APOLLO and LUNAR; N = 840 total) found that latanoprostene bunod 0.024% administered once daily led to greater reductions in mean IOP when compared to timolol maleate 0.5% (beta-adrenergic antagonist) administered twice daily at all evaluation time points (IOP was measured at 8 AM, 12 PM, and 4 PM at week 2, week 6, and months 3, 6, 9, and 12) [p < 0.001 for all] (*Weinreb et al 2018*). A greater proportion of patients treated with latanoprostene bunod vs timolol attained a mean IOP ≤ 18 mm Hg and an IOP reduction ≥ 25% from baseline (p < 0.001). Patients who switched over from timolol to latanoprostene bunod also experienced additional IOP lowering (p ≤ 0.009). Efficacy was maintained through 12 months of therapy.
- Latanoprostene bunod was also evaluated in a 28-day, Phase 2, randomized, investigator-masked, AC, MC, dose-ranging study (n = 413). The objective of the study was to assess the efficacy and safety of latanoprostene bunod vs latanoprost 0.005%, and to determine the optimum drug concentration(s) of latanoprostene bunod in reducing IOP. Patients were randomized into 1 of 5 treatment groups, including 4 different concentrations of latanoprostene bunod (0.006%, 0.012%, 0.024%, and 0.040%) and latanoprost 0.005% *(Weinreb et al 2015)*.
  - Efficacy for latanoprostene bunod was dose-dependent and reached a plateau at 0.024% to 0.040%. Latanoprostene bunod 0.024% led to significantly greater reductions in mean diurnal IOP compared with latanoprost 0.005% at day 28 (-9 mmHg vs -7.77 mmHg, respectively; p = 0.005).
  - A significantly greater proportion of patients had mean diurnal IOP ≤ 18 mmHg in the latanoprostene bunod 0.024% group at all measurement time points (p ≤ 0.046) compared to the latanoprost group.
- Available trials suggest that tafluprost may have a similar IOP-lowering effect as latanoprost, but less than that of travoprost *(Konstas et al 2013, Schnober et al 2010, Traverso et al 2010, Uusitalo et al 2010[b])*.
  - One trial found no significant difference in IOP reduction from baseline between tafluprost and travoprost following 6 weeks of treatment (difference, 0.17 mm Hg; 95% CI: -1.268 to 1.608; p = 0.811) *(Traverso et al 2010)*.
  - In a 6-week crossover trial, travoprost significantly reduced IOP from baseline compared to tafluprost (7.2 vs. 6.6 mm Hg; p = 0.01). Adverse events were similar between the treatment groups *(Schnober et al 2010)*.
  - In a randomized, double-blind trial (N = 533), tafluprost demonstrated noninferiority to latanoprost after 24 months (p < 0.05). No difference in the incidence of adverse events was reported between treatments *(Uusitalo et al 2010[b])*.
  - Results from a similar trial demonstrated a significantly lower incidence of ocular irritation/burning, tearing, itching, dry eye sensation, and conjunctival hyperemia when switched from latanoprost to tafluprost due to ocular intolerance (p < 0.001 for all). Tafluprost also significantly reduced IOP compared to baseline treatment with latanoprost (16.4 vs. 16.8 mm Hg; p = 0.049) *(Uusitalo et al 2010[a])*.
  - In a non-interventional trial by Erb and colleagues, patients with an inadequate response with prior glaucoma treatments achieved a significantly lower IOP after switching to tafluprost treatment for 6 to 12 weeks compared to baseline (16.4 ± 2.9 vs. 19.5 ± 4.4 mm Hg; p < 0.001) *(Erb et al 2011)*.
- In a trial comparing bimatoprost 0.03% and travoprost, the mean reduction in IOP was significantly greater with bimatoprost 0.03% at 9 AM (p < 0.014), but not at 1 PM (p = 0.213) or 4 PM (p ≥ 0.207) *(Cantor et al 2006)*. The results of a meta-analysis demonstrated that reductions in IOP were significantly greater with bimatoprost 0.03% compared to travoprost at 8 AM (p = 0.004) and 12 noon (p = 0.02), but not at 4 PM (p = 0.19) or 9 PM (p = 0.07). Bimatoprost 0.03% also demonstrated greater reductions in IOP compared to latanoprost at all time points. There were no statistically significant differences between latanoprost and travoprost at any time point *(Aptel et al 2008)*. In a trial evaluating bimatoprost 0.03%, latanoprost, and travoprost, the mean changes in IOP were comparable between all treatment groups at week 12 (p = 0.128); however, latanoprost was associated with fewer adverse events compared to bimatoprost (p < 0.001) *(Parrish et al 2003)*. In a meta-analysis of peak and trough IOP measurements, bimatoprost 0.03% demonstrated greater reductions in peak IOP compared to latanoprost; however, reductions were larger with latanoprost at the trough measurement *(Cheng et al 2009[a])*. Results from a similar meta-analysis by Li et al did not demonstrate a significant difference in IOP reductions between bimatoprost 0.03% and travoprost (p = 0.8) or latanoprost and travoprost (p = 0.07) *(Li et al 2006)*.
- A meta-analysis of 13 trials evaluating adverse events associated with the ophthalmic prostaglandin analogs showed that latanoprost had a lower incidence of conjunctival hyperemia compared to both bimatoprost 0.03% and travoprost (p < 0.0001 for both) *(Honrubia et al 2009)*. One trial evaluated the use of travoprost without the preservative benzalkonium chloride (BAK) and demonstrated a lower incidence of hyperemia compared to travoprost with BAK

(p-values not reported) *(Lewis et al 2007)*. The results from a second trial showed that travoprost without BAK was associated with lower Ocular Surface Disease Index (OSDI) scores compared to bimatoprost 0.03% and latanoprost ($p < 0.0001$) *(Henry et al 2008)*.

- The ophthalmic prostaglandin analogs have consistently demonstrated comparable or greater efficacy when compared to various combination therapies *(Cheng et al 2009[b], Coleman et al 2003, Fechtner et al 2004, Konstas et al 2008, Lesk et al 2008, Ozturk et al 2007, Sharpe et al 2008)*. Bimatoprost 0.03% significantly reduced IOP compared to dorzolamide/timolol in a 6-week crossover trial ($p = 0.03$) *(Sharpe et al 2008)*. In a meta-analysis of 14 trials, treatment with latanoprost or fixed-dose dorzolamide/timolol was associated with a similar reduction in IOP after 6 months ($p = 0.28$) *(Cheng et al 2009[b])*.
- In a randomized controlled trial, treatment with latanoprost was associated with greater reductions in IOP compared to betaxolol, carteolol, and nipradilol ($p < 0.05$ for all) *(Ikeda et al 2008)*. In addition, a meta-analysis of 11 randomized controlled trials showed significant reductions in IOP with latanoprost compared to timolol ($p < 0.001$) *(Zhang et al 2001)*. The ophthalmic prostaglandin analogs have consistently shown greater efficacy in reducing IOP compared to agents in other ophthalmic classes used as monotherapy *(Parrish et al 2003, Webers et al 2007, Zhang et al 2001)*. Only brimonidine reduced IOP to a similar degree as ophthalmic prostaglandin analog monotherapy ($p = 0.3$ vs. latanoprost) but with a higher incidence of adverse events (31 vs. 21%; $p = 0.0005$) *(Sonty et al 2008)*. The results from a meta-analysis by Cheng and colleagues demonstrated that brimonidine had the largest reduction in IOP at peak compared to all other glaucoma agents; however, brimonidine also had the smallest reduction in IOP at the trough time point *(Cheng et al 2009[a])*.

CLINICAL GUIDELINES

- Guidelines published in 2010 by the AOA (currently under review per the AOA website) do not recommend preferential use of any drug class, although current guidelines by the AAO generally recommend ophthalmic prostaglandin analogues as first-line pharmacologic therapy in patients with elevated IOP *(AOA 2010, Prum et al 2016)*.
- The AAO 2016 guidelines on primary open-angle glaucoma state that prostaglandin analogs are the most frequently prescribed initial eye drops because they are the most efficacious, well-tolerated products, and are administered once daily. The AAO guidelines do not recommend one ophthalmic prostaglandin analog over another *(Prum et al 2016)*.

SAFETY SUMMARY

- Class warnings include the risk of hyperpigmentation of ocular tissues and eyelash changes with darkening and thickening of eyelashes. Drugs in this class should be used with caution in patients with intraocular inflammation or macular edema. Patients should remove contact lenses prior to instillation and reinsert 15 minutes following the administration of all agents in this class except tafluprost, for which no information relating to contact lenses is available in the labeling.
- The most frequently reported adverse events associated with these agents are ocular in nature and include burning/stinging, hyperemia, pruritus, iris pigmentation changes, and growth and darkening of eyelashes.

DOSING AND ADMINISTRATION

- Administer other topical ophthalmic medications at least 5 minutes apart from the prostaglandin analogs.

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Latisse (bimatoprost)	Ophthalmic solution/drops	Ophthalmic	Daily	Apply nightly directly to the skin of the upper eyelid margin at the base of the eyelashes using the accompanying applicators. Blot any excess solution beyond the eyelid margin. Dispose of the applicator after one use. Repeat for the opposite eyelid margin using a new sterile applicator.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				May be used in patients aged ≥ 5 years for hypotrichosis of the eyelashes. Bimatoprost has been studied in patients aged 5 to 17 years who were post-chemotherapy or had alopecia and ages 15 to 17 years with hypotrichosis not associated with a medical condition. Pregnancy: Unclassified†
Lumigan (bimatoprost) 0.01%; generic bimatoprost 0.03%	Ophthalmic solution/drops	Ophthalmic	Daily	Instill 1 drop into affected eye(s) once daily in the evening; the dosage should not exceed once daily. Use in pediatric patients < 16 years of age is not recommended due to potential safety concerns related to increased pigmentation following long-term chronic use. Pregnancy: Unclassified†
Travatan Z (travoprost)	Ophthalmic solution/drops	Ophthalmic	Daily	Instill 1 drop into affected eye(s) once daily in the evening; the dosage should not exceed once daily. Use in pediatric patients < 16 years of age is not recommended due to potential safety concerns related to increased pigmentation following long-term chronic use. Pregnancy Category C
Xalatan (latanoprost)	Ophthalmic solution/drops	Ophthalmic	Daily	Instill 1 drop into affected eye(s) once daily in the evening; the dosage should not exceed once daily. Safety and effectiveness in pediatric patients have not been established. Pregnancy Category C
Vyzulta (latanoprostene bunod)	Ophthalmic solution/drops	Ophthalmic	Daily	Instill 1 drop into affected eye(s) once daily in the

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				evening; the dosage should not exceed once daily. Use in pediatric patients < 16 years of age is not recommended due to potential safety concerns related to increased pigmentation following long-term chronic use. Pregnancy: Unclassified†
Zioptan (tafluprost)	Ophthalmic solution/drops	Ophthalmic	Daily	Instill 1 drop into affected eye(s) once daily in the evening; the dosage should not exceed once daily. Use in pediatric patients is not recommended due to potential safety concerns related to increased pigmentation following long-term chronic use. Pregnancy Category C

† In accordance with the FDA's Pregnancy and Lactation Labeling Rule (PLLR), this product is not currently assigned a Pregnancy Category. Consult product prescribing information for details.

* Pregnancy Category C = Risk cannot be ruled out. Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

See the current prescribing information for full details

CONCLUSION

- Ophthalmic prostaglandin analogs currently available in the United States include bimatoprost, latanoprost, latanoprostene bunod, tafluprost, and travoprost. All are FDA-approved for the reduction of IOP in patients with open-angle glaucoma or ocular hypertension. Latisse (bimatoprost) is indicated to treat hypotrichosis of the eyelashes.
- Study results have demonstrated statistically significant differences in IOP-lowering ability among agents in the class. However, the differences are generally small, and the clinical significance of these differences has not been established. Bimatoprost is generally considered to have the greatest IOP-reducing effect among the ophthalmic prostaglandin analogs *(Aptel et al 2008, Cheng et al 2008, Denis et al 2007, Kammer et al 2010, Li et al 2016, Lin et al 2014, van der Valk et al 2009, Weinreb et al 2018)*.
- In addition to conjunctival hyperemia, ocular adverse events with the prostaglandin analogs include eye irritation, increase in the number and length of eyelashes, and changes in iris and lash pigmentation; the latter 2 are most notable if only 1 eye is treated. The ophthalmic prostaglandin analogs are considered to be better tolerated compared to other classes of medications used for the management of glaucoma *(Jacobs 2018)*. Tafluprost is the only agent within the class that is formulated as preservative-free and may be associated with less ocular irritation compared to the other ophthalmic prostaglandin analogs *(Uusitalo et al 2010[b])*.
- Guidelines published in 2010 by the AOA (currently under review per the AOA website) do not recommend preferential use of any drug class, although current guidelines by the AAO generally recommend ophthalmic prostaglandin analogues as first-line pharmacologic therapy in patients with elevated IOP *(AOA 2010, Prum et al 2016)*.
- The results from various meta-analyses have demonstrated that prostaglandin analogs reduce IOP by up to 35% and to a further extent compared to alpha$_2$-adrenergic agonists, beta adrenergic antagonists, carbonic anhydrase inhibitors, and other recommended therapies *(van der Valk et al 2009)*. Combination therapy with agents from other therapeutic classes should be used if the reduction in IOP on monotherapy is unsatisfactory *(AOA 2010, Prum et al 2016)*.

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