Drug Class Review: **Ophthalmic Prostaglandin Analogs**

VHA Pharmacy Benefits Management Strategic Healthcare Group
and the Medical Advisory Panel
Prepared by: Kathryn Tortorice, Pharm.D., BCPS

Objectives

To review the efficacy, safety, and administration of currently available ophthalmic preparations of the prostaglandin analogs used in the management of glaucoma.

Table 1: Currently Available ophthalmic Prostaglandin Analogs[1-6]

Generic Name	Trade name	Strength, package size	Manufacturer
Bimatoprost	Lumigan®	0.03%, 2.5 and 5 ml	Allergan
Travoprost	Travatan®	0.004%, 2.5 ml, twin 2.5ml unit	Alcon
Unoprostone	Rescula®	0.15%, 5ml	CIBA
Latanoprost	Xalatan®	0.005%, 2.5 ml	Pharmacia

I. Introduction[7-20]

Glaucoma can be described as a chronic ocular disorder characterized by the following features: progressive optic neuropathy (excavation of the optic nerve head and loss of visual field), with or without associated elevated intraocular pressure (IOP). In the United States it affects 15 million people resulting in 12,000 new cases of blindness per year, the second leading cause of blindness worldwide.[8] Blindness results from the death of optic nerve ganglion and is irreversible. Many factors influence the development of glaucoma. It is more prevalent in people over 40 and is five times more common in African Americans than Caucasians. Additionally, family history of glaucoma, elevated IOP, systemic vascular disease and diabetes are risk factors for glaucoma development.[15] In the past, it was believed that increased intraocular pressure (IOP) was the sole cause of visual damage. However, it is now recognized that along with increased IOP many other factors such as retinal ischemia, and reduced or deregulated blood flow may contribute to the development and progression of glaucoma. The goal in the treatment of glaucoma is to prevent a loss of vision. There are currently no proven direct treatments for the optic neuropathy of glaucoma. Instead, treatment is focused on lowering intraocular pressure, the one risk factor that can be modified. The recent publication of the OHTS trial demonstrated that lowering IOP is useful in preventing POAG in certain populations, those at moderate or high risk such as African Americans, diabetics, etc. [19] The degree to which IOP should be lowered remains unclear however the lowering of IOP with topical antihypertensive therapy continues to be accepted as the standard of care. [16] Even less clear is the benefit of treating isolated elevations of IOP without associated optic neuropathy, although these patients are frequently treated with pharmacotherapy.[20] Several ongoing glaucoma trials sponsored by the National Eye Institute are underway, and should answer questions about benefit and magnitude of benefit over time. (See Clinical Trials Supported by the National Eye Institute, http://www.nei.gov/).

Ideally, pharmacologic therapies used in glaucoma control should prevent further loss of functional vision during a patient's life while avoiding an adverse impact on the patient's quality of

life. Topically applied ocular are usually the first step in the management of glaucoma. Currently there are five classes of medications that are used to lower eye pressure: topical cholinergic agonists, topical [beta]-adrenergic antagonists, topical adrenergic agonists, topical prostaglandin analogues, and topical and oral inhibitors of carbonic anhydrase.[13] Many of these drug classes are linked with adverse effects, poor patient acceptance and limited efficacy. This drug class review will focus on the newest class of glaucoma therapy, the topical prostaglandin analogues.

II. Pharmacology[1-6,13,21-25]

These agents bind to specific receptors within the eye to lower intraocular pressure via increasing trabecular and/or uveoscleral outflow. This results in changes to either pressure-dependent or independent outflow, respectively. Additionally, it appears that a class effect of negligible diurnal variation in IOP control and lowering is true. A major difference between the prostaglandin agents may involve the receptors that are bound by each drug.[22] The receptor at which unoprostone works has not been elucidated, however it has a low affinity for the FP receptor.[13] Both latanoprost and travoprost are synthetic analogues of prostaglandin $F_{2\alpha}$ and demonstrate affinity at the FP receptor.[21] The binding of the FP receptor allows for an alteration in the collagen content of the ciliary muscle, reducing resistance in the uveoscleral pathway.[23] Bimatoprost is a prostamide analogue. Prostamides are a naturally occurring substance, derived from anandamide a membrane lipid that act as potent ocular hypotensive agents.[24,25] Bimatoprost does not have strong affinity for the FP receptor or any other known receptors. There have been recent reports that bimatoprost may also function as a prodrug with conversion in the cornea to a free acid form which binds at the FP receptors. [26,27]

III. Indications[1-6]

These agents are all indicated for the reduction of elevated intraocular pressure in patients with open angle glaucoma or ocular hypertension who are intolerant of other intraocular pressure lowering medications or insufficiently responsive (failed to achieve target IOP over time) to another intraocular pressure lowering medication.

Bimatoprost and travoprost has not been evaluated for the treatment of angle closure, inflammatory or neovascular glaucoma.

IV. Pharmacokinetics [1-6,13,19,25]

The pharmacokinetic properties of the agents are reviewed in **Table 2**.

Table 2: Pharmacokinetics

	Bimatoprost	Latanoprost	Travoprost	Unoprostone
C_{max} in aqueous humor	Within 10 min	2 hr	Within 30 min	NR
Distribution	Plasma, approximately 88% bound	Aqueous humor- acid form for 4 hrs Plasma- one hour	Plasma-in 1 hour then rapidly eliminated	NR
Metabolism	N-deethylation and glucuronidation	*B* oxidation in liver	Esterases in the cornea	NR
elimination	67%-renal	renal	Plasma levels undetectable in 1 hour	urine
Reduction in IOP	27-31% 7-8mm Hg	23-35% 6-8mm Hg	25-30% 7-8 mm Hg	13-17%

NR- not reported

V. Clinical Efficacy

When interpreting data on efficacy, it should be noted that clinical trials have not demonstrated a priori that treating to predefined IOP targets preserves vision. Nor have there been clinical trials demonstrating that more aggressive IOP lowering targets results in preservation of vision. However, there is limited observational data that suggests that patients achieving lower IOP with combined surgical and medical treatment did result in less visual field deterioration.[28] Finally, there are no clinical trials comparing preservation of visual acuity among the different topical ophthalmic drops. Thus, all comparisons of efficacy rely on the surrogate marker of lowering IOP. Additionally, a measurement error of 1-2 mmHg may be seen in IOP measurement, thus making the relevance of findings in this magnitude of questionable clinical importance.

The standard agent used for comparison of IOP lowering effects is timolol. The prostaglandins, docosanoids and prostamides have all been measured against this standard. The docosanoid unoprostone has not demonstrated significantly better IOP reduction in comparison to timolol.[29,30] Additionally, the agent must be dosed twice daily (BID). Latanoprost has proven superiority to unoprostone in a one-month crossover trial of sixty patients.[31] Since there appears to be no compelling evidence to support an advantage of unoprostone in terms of efficacy or ease of administration, the agent will not be discussed further in terms of efficacy or side effects.

Latanoprost has been shown to be more effective or at least as effective as timolol twice daily in lowering the IOP of patients with primary open angle glaucoma (POAG) or ocular hypertension. These trials indicate an agent with once daily administration to be as effective or better than a twice-daily agent. Several meta-analysis have compared these studies. In the Hedman meta-analysis32, latanoprost treated patients had a mean reduction from baseline of 7.7$\pm$ 0.1 mm Hg in comparison to timolol treated patients with 6.5$\pm$ 0.1 mmHg. This was a statistically significant finding for latanoprost. It is also interesting to note that more latanoprost treated patients reached their target IOP than timolol treated patients. The meta-analysis by Zhang[33], collaborated the findings as well as documented the increased adverse events of iris pigmentation and hyperemia in the latanoprost group. Additionally, a trial comparing once daily timolol gel to latanoprost demonstrated a superiority of latanoprost in IOP reduction over the 24 hour period measured.[34] The benefits of latanoprost administration on circadian variation have also been documented.[39,40] **Table 3** reviews several trials of latanoprost and timolol.

Bimatoprost and travoprost given once daily have been compared to timolol dosed twice daily. Both agents showed an equal or superior efficacy to twice daily timolol. **Table 4** reviews the bimatoprost trials, **Table 5** the travoprost trials. In the Brandt trial[41] it is interesting to note that the group of patients who received bimatoprost twice daily did not achieve a greater IOP lowering effect or better tolerability than the once daily group. In a report of the pooled results from two multicenter trials of bimatoprost,[42] the IOP lowering effects of this agent were sustained over the six-month period. Additionally, there was little diurnal variation in pressure readings for the bimatoprost group. In the trials of travoprost there were a large percentage of African American patients with a range of 20.5-24.9% versus enrollments of 17-20% in the trials of latanoprost and bimatoprost.[41,42,46] Of note is a finding that travoprost reduced the IOP more effectively in this population than in the other races, in comparison to latanoprost and timolol (mean IOP at 52 weeks of 17.2, 18.6 and 20.7 mmHg respectively). However, the study was not initially powered to detect this finding, the study was not collaborated by independent sources and further investigation must be performed to confirm the effect.

Table 3
Latanoprost once-daily monotherapy versus timolol

Trial	Latanoprost	Timolol	Duration	N	Baseline IOP(SEM)		End Point IOP(SEM)	
					L	T	L	T
Diestelhorst, 1998[35]	0.005% eve	0.5% BID	1 month	46	25.2(1.2)	24.8(0.9)	20.3(0.8)	22.7(1.1)
Watson, 1996[36]	0.005% eve	0.5% BID	6 months	294	26.2(0.3)	26.5(0.3)	17.1(0.2)	17.7(0.2)
Larsson, 2001[34]	0.005% eve	0.5% gel QD	1 month	27	23.6(0.2)	24.0(0.3)	13.6(0.4)	15.2(0.4)
Alm, 1995[37]	0.005% morn or eve	0.5% BID	6 months	267	25.1(0.5)	24.6(0.3)	17.1(0.4)	17.6(0.3)
Camras, 1996[38]	0.005% eve	0.5% BID	6 months	268	24.4(NR)	24.1(NR)	17.7(NR)	19.2(NR)

Eve=evening, morn= morning, BID= twice daily, QD= once daily, L=latanoprost, T=timolol, IOP= intraocular pressure
All results are statistically significant in favor of latanoprost versus timolol

Table 4
Bimatoprost once daily monotherapy versus timolol

Trial	Bimatoprost	Timolol	Duration	N	Baseline IOP (SEM)		End point IOP (SEM)	
					B	T	B	T
Brandt, 2001[41]	0.03% QD or BID	0.5% BID	3 months	596	26.1(1.7)	25.7(1.7)	16.9(0.4)	19.0(0.3)
Sherwood, 2001[42]	0.03% QD or BID	0.5% BID	6 months	1198	26.0(0.2)	25.8(0.2)	17(0.4)	18.9(0.4)

BID= twice daily, QD= once daily, B=bimatoprost, T=timolol, IOP= intraocular pressure
All results are statistically significant in favor of bimatoprost versus timolol

Table 5
Travoprost once daily monotherapy versus timolol

Trial	Travoprost	Timolol	Duration	N	Baseline IOP		End point IOP	
					TR	TI	TR	TI
Goldberg, 2001[43]	0.0015% and 0.004% QD	0.5% BID	9 months	573	27.4	27.1	18.9	19.4
Fellman, 2002[58]	0.0015% and 0.004% QD	0.5% BID	6 month	650	27.1	27.4	19.9	20.5

BID= twice daily, QD= once daily, TR=travoprost, TI=timolol, IOP= intraocular pressure
All results are statistically significant in favor of travoprost versus timolol

There have been two head to head comparisons of the agents in this class. In a thirty-day comparison of bimatoprost and latanoprost to a vehicle placebo, DuBiner et al[44], demonstrated that bimatoprost provided good diurnal control of IOP and was well tolerated by patients. The findings of this trial did not reach statistical significance (p=0.052). This is likely due to the small sample size of the trial (N=106, with N=21 in each treatment arm). There was no difference in adverse events or withdrawals between the treatment groups. A similar trial was conducted in 232 patients over a 3-month period.[45] This trial demonstrated that target IOP of $\leq$ 17 mm Hg were more often achieved in the bimatoprost group (p=0.029) as well as diurnal measurements at month 3 being lower in the bimatoprost group ($p \leq 0.006$). There was a higher incidence of conjunctival hyperemia in the bimatoprost group but this was not responsible for more withdrawals in this population. Netland,[46] et al compared travoprost,

latanoprost and timolol in a trial of 801 patients over a period of 12 months. The findings of this trial demonstrated travoprost to be equal to latanoprost and superior to timolol in IOP reduction. The pooled IOP readings taken at 4pm demonstrated travoprost to be superior to latanoprost (p=0.0191). The previously discussed benefit of travoprost seen in African American patients was demonstrated in this trial. There was no significant difference in hyperemia and iris pigment changes between latanoprost and travoprost treated groups.

VI. Safety and Adverse Effects [1-6,13,19,32,47-56]

The major adverse effects of this therapeutic group include hyperemia, iris pigmentation changes and darkening of eyelash growth.[1-6,47,48,51] It is likely that these effects are seen in all members of the class. There may be variation in their severity. In the head to head comparisons of latanoprost, travoprost and bimatoprost there was no increase in patient withdrawal from the trial due to effects from a particular agent.[44-46] Indeed, it appears that these agents are no better tolerated than timolol. The Alm study[32], showed 6.5% of patient given latanoprost had serious adverse events, compared to 2.3% of the timolol patients. Additionally, of the latanoprost patients, 43% reported adverse systemic side events, compared to 45% of the timolol patients.

The changes seen in iris color occur slowly and are more common in patients with multicolored irides. The increase in pigmentation is not due to proliferation of melanocytes but due to an increase in melanosomes per melanocyte.[49] The iris effects are not likely to reverse when therapy is discontinued. The periorbital area may also be affected by the pigmentation changes. Eyelashes may also darken and thicken during therapy. This increased hair growth may reverse upon cessation of the drug.

The hyperemia caused by these agents may cause the most discomfort and irritation to patients. In some cases the effect will subside with continued therapy, in others it may result in discontinuation of the agent. If one prostaglandin ophthalmic agent causes the effect it may be possible that another will not. **Table 6** compares the incidence of the adverse effects seen in comparative trials with these agents. There is inadequate data from head to head trials to compare side effects among the three agents by compiling all the data. This is related to the fact that the treatment periods are different (12 vs. 3 months) as well as the study protocols. The package insert for each agent quotes respectively, 15-45% incidence for bimatoprost, 5-15% for latanoprost and 35-50% for travoprost for ocular side effects such as hyperemia, eyelash changes and increased pigmentation. The results of a physician survey were recently reported and highlight the impact of these ocular effects.[50] The survey found that hyperemia and other ocular complaints may result in increased office visits, phone calls and medication changes. The survey was not powered to detect differences among the agents nor was it published in a peer-reviewed journal. It is also possible that the use of patient education on this side effect could decrease the parameters affected in the study.

Additional ocular side effects include dry eye, blurred vision, excessive tearing, burning, and stinging, itching and foreign body sensation. These events are not significantly different among the agents and do not account for increased numbers of medication discontinuation.

There have been several reports of cystoid macular edema (CME) and/or anterior uveitis with latanoprost use.[52-55] There may be a predisposition for development of this condition in pseudophakic, aphakic or phakic eyes as there is an altered blood-retinal barrier in these instances. Other conditions, which may place patients at higher risk for CME, include cataract surgery and diabetes mellitus. Discontinuation of the medication with/without the use of steroid eyedrops typically results in resolution of the CME. The possibility of this being a class effect of the prostaglandin analogues is possible, although there have been no reports of CME with bimatoprost or travoprost.

There have been few reported systemic effects of these agents. The clinical trials of the three agents did not reveal any changes in heart rate, blood pressure, or respiratory function. There may be alterations in liver function tests with bimatoprost. This may be related to enrollment of patients in

Phase III trials who had pre-existing liver disease (defined as liver disease at baseline and/or with 1 or more abnormal liver function test (ALT, AST or Total Bilirubin at least 1.5 times the upper limit of normal) at baseline. When this population is analyzed, there was no worsening of liver function over time regardless of the patient receiving bimatoprost or a comparator agent. A single case report of a patient with worsening of angina symptoms after latanoprost administration has been reviewed.[56] The patient demonstrated the angina on three separate rechallenges. On alternate medication his glaucoma is controlled with no worsening of angina.

Table 6: Adverse effects related to prostaglandin ophthalmics

Study	Adverse effect	Timolol	Bimatoprost	Latanoprost	Travoprost
Netland[46]	Hyperemia	14%		27.6%	49.5%
	Iris pigment changes	0%		5.2%	3.1%
	Eyelash changes	3.1%		25.8%	57.1%
Gandolfi[45]	Hyperemia		36.1%	14.2%	
	Iris pigment changes				
	Eyelash changes		12.6%	4.4%	

VII. Drug Interactions[1-6]

If other topical ocular hypotensive agents are used there may be additive effects with the prostaglandin and prostamide ophthalmic agents. In fact, studies with latanoprost, bimatoprost or travoprost and topical beta-blockers have shown an additive lowering of IOP. There have been no reported clinically significant drug interactions with orally administered drugs. Further investigations are necessary to confirm this finding.

VIII. Dosage and Administration[1-6]

These agents are all recommended at a dose of one drop to the affected eye(s) once daily in the evening. They may be used concomitantly with other topical ophthalmic products but administration should be separated by at least 5 minutes.

Care should be exercised if patients receiving these medications wear contact lenses. Contact lenses should be removed prior to instillation of the eyedrops and they should remain out of the eye for at least 15 minutes after administration of the eye drop.

IX. Cost

Table 7: Cost Comparison based on VA price

Product	Package size	Measured volume	Drops/ml	Days per bottle (1 drop OU)	VA price per bottle	Cost per day
bimatoprost	2.5ml	3.3 ml	33.3	55.7	29.09	0.522
	5.0ml	5.6 ml	34.1	95.2	59.05	0.620
latanoprost	2.5 ml	3.05 ml	29.5	45.2	28.66	0.634
travoprost	2.5 ml	3.0 ml	34.6	51.6	25.56	0.495

Adapted from Fiscella [57]
VA prices current as of May 2002

X. Conclusions and Recommendations

Several new prostaglandin agents have come to market over the past 18 months. Until this point latanoprost had been the sole agent in the category. Of the newer agents, unoprostone is not considered

as efficacious or desirable as the others because of its reduced efficacy (18-22% IOP reduction) and BID dosage schedule. The other new agents, bimatoprost and travoprost, are associated with greater reductions in IOP (1-2 mm Hg) compared to timolol. Both bimatoprost and travoprost may have more hyperemia and pruritus than latanoprost, but less iris or eyelash pigment changes. Local adverse effects may result in increased physician visits or calls, but seem to be unassociated with long-term effects or increased discontinuation of medication in the clinical trials. The responder rates seen with bimatoprost and travoprost appear better than those seen with latanoprost. The effect of travoprost in the African American population may be significant but this finding needs to be confirmed with further trials. A major difference among the agents is their stability and storage restrictions. Latanoprost is the only agent that requires refrigeration; although a recently marketed physician sample with a shorter shelf life does not carry this restriction.[58] The other agents do not require refrigeration or special handling though travoprost is packaged in a foil pouch, which must be removed prior to use. **Table 8** highlights these differences among the agents.

Table 8: Stability and Packaging Comparison

	Latanoprost	Bimatoprost	Travoprost
Trade name	Xalatan® 0.005%, Pharmacia	Lumigan®0.03%, Allergan	Travatan® 0.004 %, Alcon
Stability	• Requires refrigeration prior to dispensing to maintain 36 month shelf life • Physician samples can be stored at room temp with a 12 month expiration date • Up to temp 77°F for 2 weeks or 104°F for 24 hrs, potency retained.	Studied across heat and cold extremes. Consistent potency.	Studied in accelerated heat, freeze thaw cycle, refrigeration. All consistent potency.
Pros/cons	• May require special mail handling • Patients comment on "streaming" of medication from bottle	• Larger bottle size may decrease mailing costs • No restriction on storage	• No restriction on storage • Dispensed in a pouch system • May have increased efficacy in African American population.

It is recommended that a single agent from the class, latanoprost, bimatoprost or travoprost, be listed on National Formulary. The agents have all been proven superior or equal to timolol for IOP reduction. There may be differences in side effect profile and patient perception but these have not been documented in randomized, controlled, clinical trials to result in a deleterious outcome. The possible advantage of travoprost in African American patients needs further study to document this effect.

References

1. Xalatan® (latanoprost) product information. Kalamazoo, MI: Pharmacia 2001 .
2. Travatan® (travoprost) product information. Fort Worth, TX: Alcon Pharmaceuticals 2001.
3. Lumigan® (bimatropost) product information. Irvine, CA: Allergan Inc. 2001.
4. Rescula® (unoprostone) product information. Duluth, GA:Ciba Vision 2001.
5. Hebel SK, ed. Drug Facts and Comparisons. St. Louis, MO: Facts and Comparisons Inc;2001:1283-1293.
6. McEvoy G, ed. AHFS Drug Information. Bethesda, MD: American Society of Health-System Pharmacists, 2002;2751-2767.
7. Tielsch JM, Sommer A, Katz J, et al. Racial Variations in the prevalence of primary open angle glaucoma. The Baltimore Eye Survey. JAMA. 1991;266:369-374.
8. Quigley HA. Number of people with glaucoma worldwide. Br J Ophthalmol. 1996;80:389-393.
9. Quigley HA, Vitale S. Models of open angle glaucoma prevalence and incidence in the United States. Invest Ophthalmol Vis Sci. 1991;38:83-91.

10. Pointer JS. Human intraocular pressure and its diurnal variation in healthy subjects. Ophthalmic Physiol Opt. 1999;19(suppl 2):S43-S48.
11. Asrani S, Zeimer R, Wilensky J, et al. Large diurnal fluctuations in intraocular pressure are an independent risk factor in patients with glaucoma. J Glaucoma. 2000;9:134-142.
12. Collaborative Normal Tension Glaucoma Group. Comparison of glaucomatous progression between untreated and treated patients with normal tension glaucoma and patients with therapeutically reduced intraocular pressures. Am J Ophthalmol. 1998;126:487-497.
13. Hoyng PF, van Beek LM . Pharmacological therapy for glaucoma, a review. Drugs. 2000;59:411-434.
14. Stewart WC, Chorak RP, Hunt HH, Sethuraman G. Factors associated with visual loss in patients with advance glaucomatous damage in the optic nerve head. Am J Ophthalmol. 1993;116(2):176-181.
15. Georgopoulos G, Andreanos D. Liokis N, et al. Risk factors in ocular hypertension. Eur J Ophthalmol 1997;7(4):357-363.
16. Early Manifest Glaucoma Trial: design and baseline data. Ophthalmology. 1999 Nov;106(11):2144-53
17. Drance S, Anderson DR, Schulzer M; Collaborative Normal-Tension Glaucoma Study Group. Risk factors for progression of visual field abnormalities in normal-tension glaucoma. Am J Ophthalmol. 2001 Jun;131(6):699-708
18. The relationship between control of intraocular pressure and visual field deterioration. The AGIS Investigators. Am J Ophthalmol. 2000 Oct;130(4):429-40
19. Kass MA, Heuer DK, Higginbotham EJ, et al. The Ocular Hypertension Treatment Study. Archives of Ophthalmol 2002;120(6):701-713.
20. Bohn RL, Gurwitz JH, Yeomans SM, et al: Which patients are treated for glaucoma? An observational analysis. J Glaucoma 2000; 9:38-44
21. Patel SS, Spencer CM. Latanoprost. A Review of its pharmacological properties, clinical efficacy and tolerability in the management of primary open angle glaucoma and ocular hypertension. Drugs & Aging. 1996;9(5):363-378.
22. Coleman RA, Smith WL, Narumiya S. International union of pharmacology classification of prostanoid receptors: properties, distribution and structure of the receptors and their subtypes. Pharmacol Rev. 1994;46:205-229.
23. Schachtschabel U, Lindsey JD, Weinrab RN. The mechanism of action of prostaglandins on uveoscleral outflow. Curr Opinion Ophthalmol. 2000;11:112-115.
24. Brubaker RF. Mechanism of action of bimatoprost. Surv Ophthalmol. 2001;45(suppl 4):S347-S351.
25. Woodward DF, Krauss AHP, Chen J, et al. The pharmacology of bimatoprost. Surv Ophthalmol. 2001;45(suppl 4):S337-S345.
26. Sharif NA, Williams GW, Kelly CR. Bimatoprost and its free acid are prostaglandin FP receptor agonists Eur J Pharmacol (Netherlands), Dec 7 2001, 432(2-3) p211-3
27. K.M. Maxey, J. Johnson, C.B. Camras and J. LaBrecque. The Hydrolysis Of Bimatoprost In Corneal Tissue Generates A Potent Prostanoid FP Receptor Agonist. 2002 AGS abstract
28. The AGIS Investigators: The Advanced Glaucoma Intervention Study Group (AGIS): The relationship between control of intraocular pressure and visual field deterioration. Am J Ophthalmol 2000; 130: 429-440.
29. Stewart WC, Stewart JA, Kapik BM. The effects of unoprostone isopropyl 0.12% and timolol malealte 0.5% on diurnal intraocular pressure. J Glaucoma. 1998;7(6):388-394.
30. Nordmann JP, Rouland JF, Mertz BP. A comparison of the intraocular pressure lowering effect of 0.5% timolol maleate and the docosanoid derivative of a $PGF_{2\alpha}$ metabolite, 0.12% unoprostone, in subjects with chronic open angle glaucoma or ocular hypertension. Curr med Research Opinion. 1999;15(2):87-93.
31. Aung T, Chew PT, Yip CC, et al. A randomized double-masked crossover study comparing latanoprost 0.005% with unoprostone 0.12% in patients with primary open angle glaucoma and ocular hypertension. Am J Ophthalmol. 2001;131:636-642.

32. Hedman K, Alm A, Camras CB, et al. A meta-analysis of three randomized, double masked phase III clinical studies comparing latanoprost to timolol in patients with open angle glaucoma or ocular hypertension. Presented at the European Society of Ophthalmology 1997; June, Budapest, Hungary.
33. Zhang WY, Po A, Dua HS, Azuara- Blanco. Meta-analysis of randomized controlled trials comparing latanoprost with timolol in the treatment of patients with open angle glaucoma or ocular hypertension. Br J Ophthalmol. 2001;85:983-990.
34. Larsson LI. Intraocular pressure over 24 hours after repeated administration of latanoprost 0.005% or timolol gel- forming solution 0.5% in patients with ocular hypertension. Ophthalmology. 2001;108:1439-1444.
35. Diestelhorst M, Almegard B. Comparison of two fixed combinations of latanoprost and timolol in open angle glaucoma. Graefes Arch Clin Exp Ophthalmol. 1998;236:577-581.
36. Watson P, Stjernschantz J, Beck L, et al. A six-month randomized, double masked study comparing latanoprost and timolol in open angle glaucoma and ocular hypertension. Ophthalmology. 1996;103:126-137.
37. Alm A, Stjernschantz J, the Scandinavian Latanoprost Study Group. Effects on intraocular pressure and side effects of 0.005% latanoprost applied once daily, evening or morning- a comparison with timolol. Ophthalmology. 1995;102:1743-1752.
38. Camras CB and the US Latanoprost Study Group. Comparison of latanoprost and timolol in patients with ocular hypertension and glaucoma. A six-month, masked, multicenter trial in the united States. Ophthalmology. 1996;103:138-147.
39. Racz P, Ruzsonyi MR, Nagy ZT, et al. Around the clock (circadian) intraocular pressure reduction with once daily application of 0.005% latanoprost by itself or in combination with timolol. Arch Ophthalmol. 1996;114:268-273.
40. Knstas AGP, Maltezos AC, Gandi S, et al. Comparison of 24-hour intraocular pressure reduction with two dosing regimens of lantanoprost and timolol maleate in patients with open angle glaucoma. Am J Ophthalmol. 1999;128:15-20.
41. Brandt JD, VanDenburgh AM, Chen K, et al. Comparison of once or twice daily bimatoprost with twice daily timolol in patients with elevated IOP. Ophthalmology. 2001;108:1023-1032.
42. Sherwood M, Brandt J, for the Bimatoprost study groups 1 and 2. Six-month comparison of bimatoprost once daily and twice daily with timolol twice daily in patients with elevated introcular pressure. Surv Ophthalmol. 2001;45(suppl 4):S361-S368.
43. Goldberg I, Cunha-Vaz J, Jakobsen JE, et al. Comparison of topical travoprost eye drops once daily with timolol 0.5% twice daily in patients with open angle glaucoma or ocular hypertension. J Glaucoma. In press.
44. DuBiner H, Cooke D, Dirks M, et al. Efficacy and safety of bimatoprost in patients with elevated intraocular pressure: A 30 day comparison with latanoprost. Surv Ophthalmol. 2001;45(suppl 4): S353-S360.
45. Gandolfi S, Simmons ST, Strum R, Chen K, VanDenburgh AM, for the Bimatoprost Study Group 3. Three month comparison of bimatoprost and latanoprost in patients with glaucoma and ocular hypertension. Advances in Therapy. 2001;18(3)110-121.
46. Netland PA, Landry T, Sullivan EK, Andrew R, Silver L, Weiner A, Mallick S, Dickerson J, Bergamini MV, Robertson SM, Davis AA; Travoprost Study Group Travoprost compared with latanoprost and timolol in patients with open-angle glaucoma or ocular hypertension. Am J Ophthalmol. 2001 Oct;132(4):472-84.
47. Yamamoto Y, Kitazawa Y. Iris color change developed after topical isopropyl unoprostone treatment. J Glaucoma. 1997;6:430-432.
48. Iwakuchi Y, Tanahashi T, Shirao Y. Iris pigmentation in two cases following topical installation of isopropyl unoprostone. Japanese J of Clin Ophthalmol. 1999;53:971-971.
49. Hu DN, Stjernschantz J, McCormick SA. Effect of prostaglandins A(2), E(1), F(2 alpha) and latanoprost on cultured human iridial melanocytes. Exp Eye Reas. 2000;70:113-120.
50. Stewart WC, Rhodes JS, Leech JN. Survey Assesses Red Eye and Prostaglandin Use. Review of Ophthalmol. 2002;9(4).

51. Wand M, Ritch R, Isbey EK, Zimmerman TJ. Latanoprost and periocular skin color changes. Arch Ophthalmol. 2001;119:614-5.
52. Schumer RA, Camras CB, Mandahl AK. Latanoprost and cystoid macular edema: is there a casual relation? Curr Opinion Ophthamol 2000;11(2):94-100.
53. Furuichi M, Chiba T, Abe, K, et al. Cystoid macular edema associated with topical latanoprost in glaucomatous eyes with normally functioning blood-ocular barrier. J Glaucoma 2001;10(3):233-236.
54. Warwar RE, Bullock JD, Ballal D. Cystoid Macular edema and anterior uveitis associated with latanoprost use. Experience and incidence in a retrospective review of 94 patients. Ophthalmology 1998;105:263-268.
55. Moroi SE, Gottfredsdottir MA, Schteingart MT, et al. Cystoid Macular Edema associated with latanoprost therapy in a case series of patients with glaucoma and ocular hypertension. Ophthalmology 1999;106:1024-1029.
56. Mitra M, Chang B, James, T. Exacerbation of angina associated with latanoprost. BMJ. 2001;323:783.
57. Fiscella RG. Cost Considerations in Glaucoma therapy. Presented at American Academy of Ophthalmology 2001.
58. Morgan PV, Proniuk S, Blanchard J, Noecker RJ Effect of temperature and light on the stability of latanoprost and its clinical relevance. J Glaucoma. 2001 Oct;10(5):401-5
59. Fellman Rl, Sullivan K, Ratliff M, et al. Comparison of travoprost 0.0015% and 0.004% with timolol 0.5% in patients with elevated intraocular pressure. Ophthalmology 2002;109(5):998-1008.