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Abbreviated Class Update: Ophthalmics, Glaucoma agents

Month/Year of Review: August 2012
New Drug: Tafluprost
Dossier received: Yes

End date of literature search: June 2012
Brand Name (Manufacturer): Zioptan™ (Merck)
Comparator Therapies: timolol, latanoprost

Current Status of PDL Class:

- Preferred Agents: APRACLONIDINE HCL (IOPIDINE®), BETAXOLOL HCL, BRIMONIDINE TARTRATE, BRINZOLAMIDE (AZOPT®), CARTEOLOL HCL, DORZOLAMIDE HCL/TIMOLOL MALEATE, PILOCARPINE (ISOPTO CARPINE®), PILOCARPINE HCL (PILOPINE HS®) GEL, TIMOLOL MALEATE, TRAVOPROST (TRAVATAN Z®)
- Non Preferred Agents: BRIMONIDINE/TIMOLOL (COMBIGAN®), APRACLONIDINE (IOPIDINE®), LATANOPROST, DORZOLAMIDE HCL, METIPRANOLOL, LEVOBUNOLOL, BIMATOPROST (LUMIGAN®), TRAVAPROST (TRAVATAN®)

Research Questions:

- Does any of the new information change previous conclusions regarding effectiveness and safety of glaucoma agents?
- Is tafluprost more effective or safer for the treatment of glaucoma than currently available agents?
- Are there unique patients or situations where the new agent may be more effective or safer than currently available agents?

Conclusions:

- There is moderate strength evidence that all currently used medications lower intraocular pressure (IOP) and as single agents, prostaglandins are the most effective at lowering IOP and have been shown to be better than timolol, brimonidine, and dorzolamide.
- There is low quality evidence that prostaglandins are similar in efficacy and in the extent at which they lower IOP.
- There is insufficient evidence to establish a link between the intermediate outcomes of IOP reduction, prevention of optic nerve damage, or prevention of visual field loss to the ultimate outcomes of visual impairment and vision-related quality of life.
- There is low quality evidence that the combination of dorzolamide/timolol has similar effects as prostaglandins on lowering IOP and that fixed combination therapies are equally safe and effective at lowering IOP as their non-fixed components administered concomitantly, with no statistically significant differences in reported convenience or satisfaction.
- There is low-moderate quality evidence that tafluprost is noninferior to timolol in reducing IOP and failed to demonstrate noninferiority to latanoprost in reducing IOP.
- There is insufficient direct clinical evidence to recommend a preservative-free (PF) preparation over a preservative-containing (PC) preparation except when there is evidence that the patient is allergic to the preservative, and therefore tafluprost may provide value in those patients.

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Recommendations:

- Recommend continuing to include a medication from each category including miotics, sympathomimetics, beta blockers, carbonic anhydrase inhibitors, and prostaglandin analogues as preferred on the preferred drug list (PDL).
- Recommend no changes to current PDL status based on new clinical evidence or differences in efficacy/effectiveness or harms between members within each class; recommend price comparisons in executive session for any further changes.
- Due to lack of evidence for a benefit in efficacy or safety of tafluprost over currently available prostaglandins, evaluate comparative costs with other agents.

Reason for Review:

In September 2010, the Oregon Health Resources Commission (HRC) evaluated the comparative effectiveness evidence of the drugs used for glaucoma. A Provider Synergies Review from September 2009 was the evidence source.[1] Since this review a comparative effectiveness review for the treatment of glaucoma was produced by the Agency for Healthcare Research and Quality (AHRQ) Effective Health Care Program[2] and tafluprost, another prostaglandin analog, was FDA approved in February 2012.[3]

Previous HRC Conclusions (September 2010)[1]:

- Evidence does not support a difference in efficacy/effectiveness between members of this class.
- Evidence does not support a difference in harms between members of this class.
- Consider including one medication from each category (miotics, sympathomimetics, beta blockers, carbonic anhydrase inhibitors, combination products, prostaglandin analogues).
- Consider prior authorization of prostaglandin analogues for diagnostic verification (glaucoma) to eliminate cosmetic use.

Background

Primary open-angle glaucoma (OAG) is the most prevalent type of glaucoma in the U.S. population and worldwide it is the second most common cause of blindness.[4,5] In the U.S. there is estimated that 2.2 million people in 2004 have been diagnosed with open angle glaucoma.[6] Primary open-angle glaucoma is a chronic, progressive disease that often presents with characteristic optic nerve damage, retinal nerve fiber layer defects, and subsequent visual field loss. [6] African Americans have a 4-fold higher incidence and prevalence of primary open-angle glaucoma than whites.[5]

Elevated IOP is a surrogate marker known to be a risk factor for glaucoma as well as is correlated with the worsening of glaucoma once present. Studies have shown that the reduction of IOP slows the progression of damage to the optic nerve and slows visual field loss. The ultimate outcome of treating OAG is the prevention of visual impairment and the maintenance or improvement of patient-reported outcomes like quality of life. The direct link that lowering IOP leads to preservation of vision-related quality of life and reduction in visual impairment has not been demonstrated.[3] However, glaucoma is a slowly progressive disease and publications indicate that the average untreated glaucoma patient would require more than 20 years to lower most of his/her visual field.[2] Current evidence includes studies that are of too short in duration and not enough subjects to evaluate these outcomes. Lowering the pretreatment IOP by 25% or more has been shown to inhibit progression of open angle glaucoma.[3,7] The importance of fluctuations in IOP throughout the 24-hour period on long-term outcomes for glaucoma patients is not known.[2]

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National guidelines recommend treatment to maintain IOP in a range at which the patient is likely to remain stable or at which worsening of glaucoma will be slow enough that the risk of additional intervention is not justified.[6–8] Prostanglandin analogues and beta blockers are most frequently recommended as initial therapy and if a single medication is effective in lowering IOP but the target pressure is not reached, combination therapy or switching to an alternative therapy may be appropriate.[7,8] Therapy relies on the reduction of IOP and prostaglandin analogues have been proven to be the most potent in lowering IOP (25%-33%) with very few systemic side effects.[4] Prostaglandins have minimal systemic side effects but local side effects are more common, whereas β-blockers have a number of possible systemic side effects including bronchoconstriction, bradycardia, and central nervous system effects such as depression, fatigue and loss of libido.[7]

In February 2012, the FDA approved tafluprost for the treatment of open angle glaucoma or ocular hypertension. Tafluprost is a new antiglaucoma agent that is a prostaglandin analogue that is indicated to reduce IOP in those with glaucoma or ocular hypertension. It has been studied in both PC and PF formulations, although only the PF preparation is available in the United States. An epidemiological survey was carried out from 1997 to 2003 on 9658 patients using beta-blocking eye drops.[9] This study demonstrated that the most commonly reported symptoms of foreign body sensation, dry eye sensations, tearing, and eyelid itching occurred with a significantly lower prevalence in those receiving a preservative free drop compared to a preservative drop.[9] However, there are no randomized controlled trials comparing preservative and preservative free eye drops. Guidelines from the National Institute of Clinical Excellence (NICE) recommend offering a preservative-free preparation to people only if there is evidence that the person is sensitive to the preservative and there is no direct clinical evidence to recommend a PF preparation over a PC preparation.[7] Currently the only other prostaglandin analogue that does not include the commonly used preservative benzalkonium chloride is travoprost, marketed under the brand Travatan Z™. This formulation does contain another preservative, SofZia.

Methods:

A Medline literature search for meta-analyses or randomized active-controlled trials (RCT's) comparing glaucoma agents to each other for the treatment of open angle glaucoma or ocular hypertension from the October 2011 to June 2012 was performed. The Agency for Healthcare Research and Quality (AHRQ), the Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs (VA), Dynamed and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for relevant systematic reviews. The FDA website was searched for background information from advisory committees, new indications, and safety alerts. The AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines. Randomized controlled trials will be emphasized only if evidence is lacking or insufficient from those preferred sources.

Systematic Reviews:

ARHQ

A recent comparative effectiveness was performed to summarize the evidence for the safety and effectiveness of medical, laser, and other surgical treatments for OAG in adults.[2] The comparative effectiveness review included studies and systematic reviews through a search up to October 2011. Medical treatments included prostaglandin analogs (excluding tafluprost), beta agonists, carbonic anhydrase inhibitors, alpha 2 agonists, and combination treatments. Drugs that are no longer commonly used were excluded (pilocarpine, apraclonidine, epinephrine, unoprostone, diprivaphrin, ocusert, iopidine, metipranolol).[2]

Twelve systematic reviews of medical interventions were included. The most common comparisons included head-to-head comparisons of prostaglandin analogues, prostaglandin analogues compared to timolol, latanoprost compared to brimonidine, and timolol compared to brimonidine. There were no studies of

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medical therapy addressing outcomes relating to reducing visual impairment and the studies addressing change in visual acuity as a secondary outcome were of too short a duration to answer this question. There was also insufficient evidence to determine effectiveness of agents in patient-reported outcomes and quality of life or that treatments influence patient quality of life. [2]

There was low quality of evidence that prostaglandins lower IOP better than dorzolamide (carbonic anhydrase inhibitor, 2.64 mmHg, 3 trials, brimonidine (alpha-adrenergic agonist, 1.64 mmHg, 4 trials), and timolol (beta-adrenergic blocker, 5% greater at 6 months, 4 trials) and that the combination dorzolamide/timolol has similar effect as prostaglandins. [2] The mean reduction in IOP after 3 or more months was 0.81 mmHg lower for participants receiving travoprost than timolol (95% CI, -1.16 to -0.45, four trials). The percent IOP reduction from baseline to 6 month was 5% greater at 6 months with travoprost compared to timolol (95% CI, 2.8 to 7.3, four trials). [2] Evidence from one systematic review reported no difference in the mean reduction in IOP between latanoprost and the combination of dorzolamide/timolol. One study assessed patient satisfaction with either the fixed combination of timolol and dorzolamide or the unfixed combination (separate bottles) and found no statistically significant differences in reported convenience (87% fixed combination vs. 80% unfixed; p=0.056) or reported satisfaction (87% fixed combination vs. 85% unfixed; p=0.643). [2] There was also low quality evidence that prostaglandins are similar in the extent at which they lower IOP; although some studies reported a greater drop with bimatoprost, this has not been a consistent finding. A difference was demonstrated at 3 months (RD 12; 95% CI 4 to 21, two trials) but there was no difference at 1 and 6 months between bimatoprost and latanoprost. Mean IOP reduction was similar when comparing travoprost to latanoprost from two separate systematic reviews.

Harms associated with medical treatments for OAG was also evaluated. The prostaglandins were found to produce more ocular redness than timolol and within the prostaglandin class; latanoprost was less likely to cause redness. [2] Timolol was more likely to result in systemic side effects like shortness of breath or bradycardia, though these are rarely severe, and a systematic review found that subjects on timolol were less likely to drop out of studies due to side effects than those on brimonidine, latanoprost, travoprost, or betaxolol. However, the overall strength of the evidence was graded as insufficient to make conclusions of differential harms for one therapy compared to another. [2]

New Drug Evaluation: Tafluprost

FDA Approved Indications: Tafluprost ophthalmic solution 0.0015% is a prostaglandin analog indicated for reducing intraocular pressure in those with open-angle glaucoma or ocular hypertension.[3]

Efficacy: FDA approval of tafluprost was based on three phase III, randomized, non-inferiority efficacy trials in patients with a baseline IOP of 23-26 mmHg with open-angle glaucoma or ocular hypertension. [10–13] Two were published, including a fair quality 12-week study comparing preservative free (PF) tafluprost with PF timolol and a 24-month fair to poor quality study comparing preservative-containing (PC) tafluprost and PC latanoprost.[10,11] Details of these studies are found in the following evidence table. A third, unpublished trial, compared PC tafluprost to PC timolol over 12 months. Only one of these trials was conducted in sites in the US, the other trials were all conducted in sites outside of the US, mostly in Europe. The primary outcome in the studies was change in baseline IOP and a pre-specified a non-inferiority limit of 1.5 mmHg for the upper limit of the 95% CI was used to establish non-inferiority, as this is the standard acceptance level of non-inferiority in glaucoma studies.[13] The FDA medical reviewer concluded that “a 1.5 mmHg non-inferiority margin for a non-inferiority study using timolol as the active comparator seems reasonable.”[12] . Studies using the PC tafluprost also served as support for drug approval as a result of a pharmacodynamic study conducted by Hamacher, et al. designed to demonstrate the equivalence of the two formulations (PC and PF).[14] This 8 week, investigator masked, randomized

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trial demonstrated similar IOP-lowering effects at week 1 and 4, meeting the 1.5 mmHg non-inferiority margin.[14] The PC formulation of tafluprost is only available in countries outside the United States.

A study by Chabi et al. was a 12-week trial comparing PF tafluprost and PF timolol.[10] Both products showed IOP lowering effects throughout the 12 weeks, and the effects of tafluprost met the pre-specified non-inferiority margin of 1.5 mmHg compared to PF timolol at all visits and time points. [10] More than half of the patients had ≥25% reduction in diurnal IOP from baseline in both treatment groups (secondary endpoint). A per protocol population was used for analysis of the efficacy end point in which patients who violated pre-specified criteria were excluded. The authors declared that the results were also similar using an analysis based on a full analysis set population (including all randomized patients who received at least 1 dose of study treatment and had at least 1 efficacy measurement available for the analysis endpoint), and the FDA medical reviewer confirmed that using the full analysis set, the confidence interval was within 1.5 mmHg at all time points.[12] It is unclear how many patients were excluded from the full analysis set population. Missing IOP data were imputed by carrying the last observation forward from previous treatment visits. The between group differences in mean IOP change from baseline at each time point at week 12 was generally consistent among the subgroups that were defined by age, race, sex, baseline IOP, and ocular diagnosis. [10]

Another fair quality randomized study by Usitalo et al. was a 24-month multinational trial comparing PC tafluprost with PC latanoprost; both preserved with benzalkonium chloride.[11] Both tafluprost and latanoprost had a substantial IOP-lowering effect throughout the study; on average 6-8 mmHg and 7-9 mmHg, respectively. [11] This result was seen by week 2 and was continued up to the month 24 visit. However, for the primary outcome of reduction in IOP, tafluprost failed to meet the pre-specified non-inferiority margin of 1.5 mmHg (1.20 mmHg with the upper 95% CI limit of 1.52) versus latanoprost.[11] At month 24, the mean decrease in IOP from baseline was -7.1 mmHg (29.1%) and -7.7 mmHg (32.2%) for tafluprost and latanoprost, respectively. There was a statistically significant difference in the lack of efficacy discontinuation rates in favor of latanoprost (13 vs. 3, p=0.01) and this may have been due to more people in the tafluprost group being more treatment resistant and prior to the trial requiring both prostaglandins and β-blockers concurrently, as well as a slightly higher baseline IOP. [11] According to the dossier submission, the proportion of responders at 6 months was somewhat smaller in the tafluprost group compared to the latanoprost group (≥20% decrease: 80.3% vs. 89.9%; ≥25% decrease: 62.8% vs. 79.0%; ≥30% decrease: 46.4% vs. 67.3%).[13]

The third, unpublished trial compared PC tafluprost with PC timolol in 458 patients over 12 months, randomized at a ratio of 3:2 in centers only in the United States.[3,12] Treatments were masked to the subject, investigator, and site staff. There was a total attrition rate of 12% and 17 (6.4%) discontinued the study in the tafluprost group and 23 (12.0%) in the timolol group. In the modified intention to treat (ITT) analysis, the estimated overall treatment difference at 6 months was -0.28 mmHg (upper 95% CI =0.21 mmHg). [3,12] The results of mean IOP's met the pre-defined 1.5 mmHg margin of noninferiority and most 95% CI limits were within a 1 mmHg margin.. The proportion of responders with a ≥25% decrease in mean diurnal IOP were similar between the two groups (43.8% tafluprost vs. 46.2% timolol, p=0.69). This study also demonstrated more ocular adverse events for patients treated with tafluprost (50.9%) compared to timolol (44%).[3, 11]

Lastly, a fair quality study by Egorov et al. evaluated the efficacy and safety of tafluprost as adjunctive therapy to timolol in prostaglandin naïve patients who were only partially controlled with timolol.[15] At the 6-week time point the timolol-tafluprost group showed an IOP reduction of 5.5 to 5.8 mmHg compared to the timolol-vehicle group that showed an IOP reduction of 4.0 to 4.2 mmHg. [15] The effect seen in this study is in line with previous studies that investigate the addition of prostaglandin analogues as adjunctive therapy to patients uncontrolled by timolol monotherapy.[12]

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Safety: In general tafluprost was well tolerated and there was no occurrence of any serious adverse events. According to the FDA medical review, most adverse events were of mild severity.[12] The rates of adverse events were not significantly different between tafluprost, timolol, and latanoprost. In the study between PF tafluprost and PF timolol, the tafluprost group had significantly higher rate of conjunctival hyperemia than the timolol group (4.4% vs. 1.2%, p=0.016).[10] The most common adverse events that were reported in the tafluprost group were ocular hyperemia (11%), ocular stinging/irritation (7%), ocular pruritis (5%), dry eye (3%), ocular pain (3%), eyelash darkening (2%), growth of eyelashes (2%), blurred vision (2%), headache (6%), common cold (4%), cough (3%), and urinary tract infection (2%).[12] The most common non ocular event was headache. When investigated, there were no clinically significant differences identified for effects of age, gender, race, prior prostaglandin use, baseline IOP, central corneal thickness, and iris color. [12]

COMPARATIVE CLINICAL EFFICACY

Relevant Endpoints

Preservation of visual function
Maintenance of quality of life
Withdrawal due to adverse events

Study Endpoints

Primary: Difference in change in IOP from baseline
Secondary: Proportion of patients with ≥25% reduction in diurnal IOP from baseline

Evidence Table

Ref/ Study Design[1]	Drug Regimens[2]	Patient Population	N	Duration	Efficacy Results[3] (CI, p-values)	ARR/ NNT[4]	Safety Results (CI, p-values)	ARI/ NNH[4]	Quality Rating[5]; Comments

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1. Chabi A, et. al[8] Phase III, RCT, DB, PG, AC, noninferiority Study 001	PF tafluprost 1 drop QHS + placebo instilled QAM PF timolol (0.5%) 1 drop "study eye" BID x12-week Mean duration 80.6 days for PF tafluprost and 82.1 days for PF timolol	Mean Age: 63.3 yrs Female 58.3% Black 22.7% 60% primary open-angle glaucoma 40% had ocular hypertension Inclusion Criteria: >18 yrs, Mean IOP of ≥23 and ≤36 mmHg Exclusions Criteria: Mean IOP >36, abnormal corneal sensation, significant visual field defect, history of ocular surgeries, ocular medications other than anti-glaucoma medications within 1 week of screening, significant CV disease, asthma or a history of pulmonary disease, allergic conjunctivitis	PF tafluprost: 320 PF timolol: 323	IOP was measured at baseline, 3 times during the day (08:00, 10:00 and 16:00) on weeks 2, 6, and 12 Noninferiority margin of 1.5 mmHg at each of the 9 time points assessed	<u>Difference in change in IOP from baseline (least squares mean) at 0800, 1000, and 1600*</u> *Week 2* -0.4 (-0.8, 0.1)*, -0.7 (-1.1, -0.3)* -0.8 (-1.3, -0.4)* *Week 6* 0.1 (-0.3, 0.6)* -0.4 (-0.9, 0.0)* -0.8 (-1.3, -0.3)* *Week 12* 0.0 (-0.4, 0.5)* -0.4 (-0.9, 0.0)* -0.6 (-1.0, -0.1)* *The criterion for declaring PF tafluprost noninferior to PF timolol was met since all the upper limits of the 95% CIs were less than the prespecified noninferiority margin of 1.5 mm Hg. <u>Proportion of patients with ≥25% reduction in diurnal IOP from baseline to week 12:</u> *Taf:* 178/298 (59.7%) 95% CI (53.9 – 65.3) Tim: 173/312 (55.4%) 95% CI (49.7-61.0) RR 0.93; 95% CI (0.8 to 1.1) P=0.3	NA NS	<u>Discontinuations due to adverse event</u> Taf: 4/320 (1.3%) Tim: 3/323 (0.9%) P=0.695 RR 1.3; 95% CI (0.23 - 7.5) <u>Conjunctival hyperemia</u> Taf: 14 (4.4%) Tim: 4 (1.2%) P=0.016 RR 3.5; 95% CI (1.1 to 12.6)	NS ARI 3.2% NNH 31	**Quality Rating**: Fair; **Internal Validity**: RoB: <u>Selection</u> – Appropriate methods for randomization sequence generation and concealment of allocation. More patients in the tafluprost group had prior prostaglandin use at baseline (59.7% vs. 55.1%), and consistently on almost all ophthalmologic medications. <u>Performance</u> – Patients and investigators masked to treatment allocation/ Identical unit dose containers used. Patients randomized to PF tafluprost received masked PF vehicle in the morning pouches and active PF tafluprost in the evening pouches, and patients randomized to timolol received unit dose pouches marked for morning and evening administration. Good compliance. <u>Detection</u>-Merck monitoring staff and site staff masked to treatment <u>Attrition</u> – Per protocol population used for primary efficacy analysis and 31 patients (4.8%) were excluded (21 in tafluprost group, 10 in timolol group). More patients excluded in tafluprost group due to medical history and receiving incorrect study medication. LOCF used to impute missing data (7.1% data imputed for tafluprost and 3.9% for timolol). **External Validity** <u>Recruitment</u> – not reported <u>Patient Characteristics –</u> Extensive exclusion criteria, a threefold higher prevalence of glaucoma occurs in African Americans and only 22.7% of patients in study <u>Setting</u> – multinational sites <u>Outcomes</u> - Surrogate endpoints utilized. No quality of life or visual acuity outcomes measured. Unclear how to relate LSM outcome to clinical relevance.

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2. Uusitalo, et. al[9] Phase III, RCT, DB, PG, AC, noninferiority Study 74458	PC tafluprost (0.0015%) 1 drop QHS PC latanoprost (0.005%) 1 drop QHS X24-months (initially a 12-month study then extended)	Mean Age: 62.5 yrs 99% Caucasians 56% primary open-angle glaucoma 37% had ocular hypertensior Inclusion Criteria: ≥18 yrs w/ diagnosis of primary open-angle glaucoma, capsular glaucoma, pigmentary glaucoma or ocular hypertension, an untreated IOP of 22/34 mmHg (after washout if applicable) in at least one eye and ETDRS visual acuity score of +0.6 logMAR (Snellen equiv 20/80) or better in each eye Exclusion Criteria: Pregnant, any uncontrolled systemic disease, IOP >34mmHg, active ocular disease, advanced visual fiel defect, use of any other antiglaucoma medications, current alcohol or drug abuse.	PC taf: 269 PC lat: 264	Assessed at baseline and at 2 and 6 weeks, and 3 6, 9, 12, 12.5-13, 15, 18 and 24 months Noninferiority margin of 1.5 mmHg	<u>Overall diurnal IOP from baseline at 24 months</u> taf: -7.1 mmHg (29.1%) lat: -7.7 mmHg (32.2%) Mean Difference in IOP *Estimated overall difference(tafluprost – latanoprost; ITT population):* 1.20 mmHg; upper CI of 1.52 (RM-ANCOVA*) 0.95 mmHg; upper CI of 1.38 (RM-ANOVA*) *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% confidence intervals 1.38 and 1.52 for the overall period, respectively). The noninferiority limit was 1.5 mmHg. <u>Proportion of patients with ≥25% reduction in diurnal IOP from baseline to 6 months*:</u> Taf: 62.8% Lat: 79.0% *From Merck Dossier (raw data not available)	NA/NS NA/NS NA*	<u>Withdrawals due to adverse events:</u> taf: 6/269 (2.2%) lat: 5/264(1.9%) p=0.8 RR 1.2; 95% CI (0.3-4.4) <u>Overall Attrition:</u> Taf:84/269 (31%) Lat: 47/264 (18%) P<0.001 RR 1.75; 95% CI (1.2-2.5) <u>Conjunctival hyperemia</u> Taf: 11/264 (4.2%) Lat: 4/264 (1.5%) P=0.073 RR 2.7; 95% CI (0.9-10.2) <u>Ocular Adverse Events:</u> taf: 127/264 (48.1%) lat: 117/264 (44.3%) p=0.503 RR 1.1; 95% CI (0.9 to 1.3)	NS N/A NS NS	**Quality Rating**: Fair **Internal Validity**: RoB: <u>Selection</u> – Unclear randomization sequence generation and allocation concealment. Slightly more prior use of anti-glaucoma meds requiring washout in tafluprost group (77% vs. 73%) and a worse mean IOP in tafluprost group, more treatment resistant patients in tafluprost group <u>Performance</u> –low risk; blinding of patients and investigators <u>Detection</u>- unclear blinding of evaluators <u>Attrition</u> – Overall 25% attrition rates in full 13-month period with higher rate in tafluprost: **External Validity** <u>Recruitment</u> – not reported <u>Patient Characteristics –</u> 3 fold highe incidence of glaucoma in African Americans than Caucasians – this study included >99% Caucasian patients <u>Setting</u> – multinational <u>Outcomes</u> – Surrogate endpoint of change in IOP measured -More discontinuations due to lack o efficacy in tafluprost group (13 vs. 3; p=0.01).

[1]**Study design abbreviations:** DB = double-blind, RCT = randomized trial, PC = placebo-controlled, PG = parallel -group, XO = crossover, DM = double-masked, AC = active-controlled [2]**Drug Regimens:** PF = preservative-free, PC = preservative-containing, IOP = intraocular pressure, PG = prostaglandin, ETDRS = Early Treatment Diabetic Retinopathy Study, Taf = Tafluprost, Lat = Latanoprost, Tim = Timolol [3]**Results abbreviations**: RRR = relative risk reduction, RR =relative risk, OR= Odds Ratio, HR = Hazard Ratio, ARR = absolute risk reduction, NNT = number needed to treat, NNH = number needed to harm, CI = confidence interval, ARI = absolute risk increase [4]**NNT/NNH** are reported only for statistically significant results [5]**Quality Rating:** (Good- likely valid, Fair- likely valid/possibly valid, Poor- fatal flaw-not valid)

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Appendix 1: Specific Drug Information

CLINICAL PHARMACOLOGY

Tafluprost is a prostaglandin analog that is selective for the FP prostanoid receptor agonist. The exact mechanism is unknown but it is thought that it decreases intraocular pressure by increasing uveoscleral outflow.[1]

DRUG SAFETY

Serious (REMS, Black Box Warnings, Contraindications): Currently there are no contraindications listed for tafluprost. This drug should only be used to treat conditions in which there is an increase in intraocular pressure.[1]

Tolerability (Drop-out rates, management strategies): According to the FDA review, a total of 94 (10.4%) in the tafluprost group, 41 (7.6%) in the timolol maleate group, and 25 (8.0%) in the latanoprost group withdrew from the phase III trials mostly due to adverse event, lack of efficacy, and patient request.[12] Of those discontinuations a somewhat higher number of patients discontinued due to lack of efficacy 23 on tafluprost (2.5%), 9 on timolol (1.7%), and 3 (1%) on latanoprost.[12]

Pregnancy/Lactation rating: C. Pregnant women were not included in the studies but studies from rats and rabbits did show tafluprost to be teratogenic when administered intravenously. The manufacturer recommends that tafluprost should not be used during pregnancy unless the potential benefit justifies the potential risk to the fetus. A study in lactating rats demonstrated that tafluprost and/or its metabolites were excreted in milk but this is not known in humans. Tafluprost should be used in caution in nursing women.[1]

Dose Index (efficacy/toxic): In two phase II trials doses of tafluprost ranged from 0.0003% to 0.005%, 0.0015% was selected because it has similar effects of 0.001% and 0.0025% and slightly better effects than 0.005%.[12] It was reported that no systemic toxicity was observed in several repeat-dose topical ocular studies in monkeys at 100-fold higher than anticipated in man.[12]

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Adverse event comparison between tafluprost, timolol, and latanoprost[1, 12]

ADE	Tafluprost n (%)	Timolol n (%)	Latanoprost n (%)
	N=905	N=543	N=311
OCULAR			
Conjunctival hyperemia	97 (10.7)	23 (4.2)	22 (7.1)
Ocular stinging/irritation	65 (7.2)	38 (7.0)	22 (7.1)
Ocular pruritus	44 (4.9)	11 (2.0)	5 (1.6)
Ocular pain	31 (3.4)	15 (2.8)	6 (1.9)
Dry eye	27 (3.0)	11 (2.0)	9 (2.9)
Growth of eyelashes	21 (2.3)	0 (0.0)	11 (3.5)
Blurred vision	19 (2.1)	15 (2.8)	2 (0.6)
Eyelash darkening	15 (1.7)	0 (0.0)	9 (2.9)
NONOCULAR			
Headache	51 (5.6)	15 (2.8)	15 (4.8)
Common cold	36 (4.0)	13 (2.4)	8 (2.6)
Cough	27 (3.0)	9 (1.7)	7 (2.3)
UTI	18 (2.0)	6 (1.1)	2 (0.6)

DOSE & AVAILABILITY[1]:

STRENGTH	FORM	ROUTE	FREQUENCY	RENAL ADJ	HEPATIC ADJ	Pediatric Dose	Elderly Dose	OTHER DOSING CONSIDERATIONS
0.0015%	Solution	Ophthalmic	1 drop once daily in the evening	No adjustment	No adjustment	Not recommended due to safety concerns related to increased pigmentation following long-term chronic use	No differences in safety or effectiveness	If other medications are to be used in the eye waiting at least 5 minutes between Store unopened foil pouches in refrigerator

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PHARMACOKINETICS[1]

Parameter	Result
Onset of action	2-4 hrs
Absorption	Through the cornea
Peak effect	~12 hrs
Cmax	26pg/mL
Half-Life	30 minutes
Metabolism	Ester prodrug hydrolyzed to active acid metabolite in the eye, further metabolized via fatty acid β-oxidation and phase II conjugation

ALLERGIES/INTERACTIONS

Drug-Drug: Tafluprost does not have any specific drug-drug interactions listed. However if other medications need to be instilled in the eye, then the patient should wait five minutes between the instillations.[1]

Food-Drug: Tafluprost is not affected by food.[1]