Tafluprost 0.0015% Ophthalmic Solution (Zioptan)

National PBM Drug Monograph

VA Pharmacy Benefits Management Services,
Medical Advisory Panel, and VISN Pharmacist Executives

*The purpose of VACO PBM-SHG drug monographs is to provide a comprehensive drug review for making formulary decisions.  These documents will be updated when new data warrant additional formulary discussion.  Documents will be placed in the Archive section when the information is deemed to be no longer current.*

**Executive Summary**

* Tafluprost is the 4th prostaglandin analogue (PGA) for reducing elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension. It is the first preservative-free (PF) PGA available in the US.
* The recommended dose is one drop in affected eye(s) once daily in the evening.
* Tafluprost must be stored in the refrigerator (36-46°F) in the original pouch. Once the pouch is opened, the single-use containers may be stored in the opened foil pouch for up to 28 days at room temperature (68-77°F). Protect from moisture. Discard any unused containers 28 days after first opening the pouch.
* Most clinical trials were conducted using a preservative-containing (PC) formulation of tafluprost. A 4-week bridging study found lowering of intraocular pressure (IOP) with the PF formulation to be equivalent to the PC formulation; therefore, the FDA was able to consider the studies using the PC formulation to support approval of the PF formulation.
* Reduction of IOP was the primary efficacy outcome in the Phase 3 trials. Three active comparator trials found tafluprost to be non-inferior to timolol 0.5% and latanoprost.
* Four small, 12-week, non-randomized, open-label trials evaluated switching patients with tolerability issues to their current BAK-preserved PGA to tafluprost PF. The IOP lowering effect was maintained after the switch and some subjective and objective measures of dry eye were improved.
* The role of preservatives, particularly benzalkonium chloride (BAK), causing ocular toxicity has been demonstrated in *in vitro* studies using cell culture lines and animal studies; however, significance in the human eye is debated. Evidence comparing the same drug entity using BAK versus no preservative or switch studies as mentioned above showed some improvement in adverse events; however, results were inconsistent.
* As with the other PGAs, tafluprost has the following warnings/precautions: increased pigmentation of the iris, eyelid, and eyelashes; eyelash changes (increased length, thickness, number); cautionary note on use in patients with active intraocular inflammation; reports of macular edema.
* The acquisition cost of tafluprost substantially exceeds that of latanoprost which is available generically. Tafluprost is also more costly than the other branded PGAs.
* Tafluprost is an option for those with documented hypersensitivity to BAK or to other PGAs.

**Introduction**

Tafluprost was approved in 2012 making it the 4th prostaglandin analogue for reducing elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension. It is the first preservative-free prostaglandin analogue available in the US.

**Pharmacology**

Tafluprost is a prostaglandin analogue, a selective FP prostanoid receptor agonist. It is believed to reduce intraocular pressure by increasing uveoscleral outflow of aqueous humor.

**FDA Approved Indications**

For reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension

**Current VA Alternatives**

Prostaglandin analogs: Lantanoprost

**Dosage and Administration**

* The recommended dose is one drop in affected eye(s) once daily in the evening.
* If more than one topical ophthalmic product is being used, each one should be administered at least 5 minutes apart.
* The solution from one individual unit should be used immediately after opening for one or both eyes. Any remaining solution should be discarded.

**How Supplied/Storage and Handling**

Tafluprost 0.0015% is supplied as a sterile solution in single-use containers packaged in foil pouches. Each foil pouch contains 10-single-use containers. Tafluprost is available in a carton of 30 and 90.

Tafluprost must be stored in the refrigerator (36-46°F) in the original pouch. Once the pouch is opened, the single-use containers may be stored in the opened foil pouch for up to 28 days at room temperature (68-77°F). Protect from moisture. Discard any unused containers 28 days after first opening the pouch.

**Efficacy**

The preservative-containing (PC) formulation of tafluprost was used for most Phase 3 trials. Three trials had an active comparator; 2 compared tafluprost to timolol1, 3 and 1 compared PC tafluprost to PC latanoprost2. Regarding the 2 studies using timolol as the comparator, 1 used the PC formulations1 and the other used the PF formulations3.

There is 1 trial using PC tafluprost as add-on therapy to timolol versus the addition of the vehicle to timolol.4

A 4-week bridging study found the PF formulation to be equivalent to the PC formulation; therefore, the FDA was able to consider the studies using the PC formulation to support approval of the PF formulation.5

Tafluprost was found to be non-inferior to timolol 0.5% and latanoprost.1-3 The addition of tafluprost to timolol was superior to timolol alone.4 (**Table 1 and Appendix** **1**).

**Table 1: Phase 3 Trials**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Duration** | **Treatment Arms** | **Baseline IOP (mmHg)** | **Change in IOP (mmHg)** |
| Study 15-003 | 12 months | PC TAF 0.0015% (n=267)PC TIM 0.5% (n=191) | **IOP at 8A/10A/4P**25.1/23.5/22.625.6/23.8/22.7 | **IOP at 8A/10A/4P**18.9/17.8/17.718.5/17.8/18.2 |
| Uusitalo 2010Study 74458 | 24 months | PC TAF 0.0015% (n=269)PC LAT 0.005% (n=264) | 24.3±3.023.8±2.8 | -7.1 -7.7  |
| Chabi 2012Study 001 | 12 weeks | PF TAF 0.0015% (n=320)PF TIM 0.5% (n=323) | 24.9±2.824.7±2.5 | -6.9 [-7.2, -6.6]-6.6 [-6.9, -6.3] |
| Egorov 2009Study 74460Adjunctive therapy | 6 weeks | PC TAF + TIM (n=96)Vehicle + TIM (n=89) | **IOP at 8A/10A/4P**24.6/23.8/23.124.6/23.6/23.3 | **IOP at 8A/10A/4P**-5.49/-5.82/-5.53-4.01/-3.99/-4.15 |
| Hamacher 2008Study 77550 | 4 weeks/arm | N=43 (cross-over study)PF TAF 0.0015% PC TAF 0.0015%  | **IOP at 8A/12P/4P/8P§**23/22/21.5/2222.5/21/22/22 | **IOP at 8A/12P/4P/8P****Tx diff PF TAF- PC TAF**0.24/0.11/0.00/-0.30 |

Abbreviations: IOP=intraocular pressure; LAT=latanoprost; PC =preservative-containing; PF =preservative-free; TAF=tafluprost; TIM=timolol

§Values estimated from graph

*Switch Trials*

Four non-randomized open-label trials have evaluated switching patients with tolerability issues to their current BAK-preserved PGA to tafluprost PF.7-10 All were 12-week trials where all patients switched to tafluprost PF. The IOP lowering effect was maintained after the switch.

Some subjective and objective measures of dry eye were improved. Mean tear breakup time (TBUT) increased after switching to tafluprost PF; however, it did not reach normal values (>10 seconds).7, 8 A marker of inflammation (HLA-DR) and mucin production (MUC5AC) was evaluated using conjunctival impression cytology samples. In those with abnormal values at baseline, the percentage of conjunctival cells expressing HLA-DR (abnormal >40%) decreased and goblet cells expressing MUC5AC (abnormal <7%) increased after switching to tafluprost PF.8 Increased tear osmolarity is a marker for dry eye disease. One study found that mean tear osmolarity was reduced after switching to tafluprost PF and that there was an improvement in fluorescein corneal staining.7 Major limitation of these studies was the lack of a control arm. (**Appendix 2**)

**Safety**

The pooled safety data are based on two Phase 2 trials (one-28 day and one 6-week trial) and three Phase 3 trials (15-003, 74458 by Uusitalo, and 001 by Chabi). Note that all studies, except the one by Chabi, used the PC formulation of tafluprost. Discontinuation of treatment due to an adverse event occurred in 2.7, 2.6, and 2.4% of patients in the tafluprost, latanoprost and timolol groups respectively.1

Ocular adverse events are shown in **Table 2**. Conjunctival hyperemia, ocular pain, ocular pruritus, and blurred vision were reported more often with tafluprost than latanoprost. Other adverse effects such as blepharitis, aggravated cataracts, and eyelash darkening and growth were reported more often with latanoprost than tafluprost. See **Appendix 3** for adverse effects broken down by individual study. The most common nonocular adverse events reported more often with tafluprost were headache (6%), common cold (4%), cough (3%), and urinary tract infection (2%).

**Table 2: Adverse Ocular Events Reported by ≥2% of Patients in any Group (%)**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Tafluprost (n=905)** | **Latanoprost (n=311)** | **Timolol (n=543)** |
| Any eye disorder | 38.6 | 40.0 | 21.7 |
| Blepharitis | 1.0 | 2.3 | 0.6 |
| Cataract aggravated | 1.0 | 4.2 | 0.0 |
| Conjunctival hyperemia | 10.7 | 7.1 | 4.2 |
| Dry eye | 3.0 | 2.9 | 2.0 |
| Eyelash darkening | 1.7 | 2.9 | 0.0 |
| Eyelash growth | 2.3 | 3.5 | 0.0 |
| Ocular pain | 3.4 | 1.9 | 2.8 |
| Ocular stinging/irritation | 7.2 | 7.1 | 7.0 |
| Ocular pruritus | 4.9 | 1.6 | 2.0 |
| Blurred vision | 2.1 | 0.6 | 2.8 |

Data obtained from FDA briefing materials

*Preservative vs. preservative-free*

The safety of preservatives used in ophthalmic products has been heavily debated. The majority of ophthalmic glaucoma products use BAK as the preservative. Studies evaluating BAK in animals and in vitro studies using cell cultures have demonstrated toxic effects to the ocular surface. Implicated toxicities include changes to the corneal and conjunctival surfaces, ocular discomfort, tear film instability, conjunctival inflammation, subconjunctival fibrosis, and epithelial apoptosis. Clinically patients may complain of dry eyes, foreign body sensation, burning, grittiness, and photophobia. Allergic manifestations may present such as conjunctival hyperemia and chemosis, lid swelling, eczema of the periorbital skin, extreme itching; however, it could be due to the drug, preservative, or excipients. There is a case report of anaphylaxis in a patient using an ophthalmic preparation containing BAK and who subsequently had a positive skin test with BAK.13

Some have argued that these types of studies do not represent what happens in the human eye. In addition to the preservative used, the medication itself, pH and osmolarity of the solution need to be considered. The number of drops and duration of use also play a role.

Ideally, head-to-head randomized clinical trials comparing the same drug preserved with BAK versus PF would be useful in determining whether or to what extent BAK contributes to the adverse effects.

There are 2 studies directly comparing the 2 formulations of tafluprost; the earlier mentioned study in patients with glaucoma or ocular hypertension5, and a study in healthy volunteers6. The glaucoma study (n=43) was a 4-week randomized cross-over study. More ocular adverse events were reported with the PF formulation. There were 16 events reported with the PF formulation compared to 6 events with the PC formulation. The most commonly reported AE was conjunctival hyperemia (6 vs. 2 respectively).5 In the healthy volunteer trial, comparable rates of conjunctival hyperemia was reported with the 2 formulations; however, the events were considered to be of moderate intensity in the PC group and of mild intensity in the PF group.6

Two other PGAs, latanoprost and bimatoprost, have compared the BAK-preserved product versus the same drug preservative-free (note that these PF products are not commercially available at this time).11, 12 Both studies were 12-weeks in duration and found that the PF product was non-inferior to the BAK-containing product in reducing IOP. There were no significant differences in safety and tolerability between bimatoprost PF and bimatoprost with BAK.12 The latanoprost study found that conjunctival hyperemia was less frequent and severe with latanoprost PF vs. latanoprost with BAK. No difference was found for other objective signs such as corneal punctate staining, anterior chamber flare, etc. In this study subjective ocular symptoms, mainly burning/stinging were significantly lower with latanoprost PF.11

All these studies were of relatively short duration and evaluated PGA monotherapy exposing patients to 1 drop of medication per day. Patients may require more than 1 agent to treat IOP, potentially increasing the exposure to BAK. It has been shown that he number of drops and the length of time over which they are used also play a role. Comparative studies of longer duration as well as in combination with other agents containing BAK are needed to assess the impact of BAK and the PF formulation on ocular toxicity

**Look-alike / Sound-alike (LASA) Error Risk Potential**

As part of a Joint Commission standard, LASA names are assessed during the formulary selection of drugs.  Based on clinical judgment and an evaluation of LASA information from three data sources (Lexi-Comp, First Databank, and ISMP Confused Drug Name List), the following drug names may cause LASA confusion:

**Table 14: Results of LASA Search**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| NME Drug Name | Lexi-Comp | First DataBank | ISMP | Clinical Judgment |
| TafluprostZioptan | NoneNone | NoneNone | NoneNone | TravoprostTamifluZolmitriptan nasal solnZirgan opth gel |

**Contraindications**

None

**Warning/Precautions**

All the PGAs have the following warnings and precautions

* Increased pigmentation of the iris, eyelid, and eyelashes
* Eyelash changes which may include increased length, color, thickness, shape and number of lashes
* Use with caution in patients with active intraocular inflammation (e.g., iritis, uveitis) because inflammation may be exacerbated
* Macular edema has been reported with use of PGAs. Use with caution in aphakic patients, in psuedophakic patients with a torn posterior lens capsule, or in patients with known risk factors for macular edema

**Drug Interactions**

None

**Pregnancy/Nursing**

Pregnancy Category C: In rat and rabbit studies, intravenously administered tafluprost was teratogenic. Tafluprost should not be used during pregnancy unless the potential benefit justifies potential risk to the fetus. Women of child-bearing potential should use adequate contraception.

Nursing: In lactating rats, tafluprost and/or its metabolites are excreted in the milk. It is not known if tafluprost and/or metabolites are excreted in human milk. Use caution if tafluprost is administered to nursing women.

**Cost**

Refer to VA pricing sources for updated information.

**Conclusion**

Tafluprost is the first preservative-free PGA. Three Phase 3 active comparator trials found tafluprost to be non-inferior to timolol 0.5% and latanoprost. Tafluprost carries warnings/precautions similar to the other PGAs: increased pigmentation of the iris, eyelid, and eyelashes; eyelash changes (increased length, thickness, number); cautionary note on use in patients with active intraocular inflammation; reports of macular edema.

Data with this product and other products comparing PF to the PC product showed similar lowering of IOP. The role of preservatives, particularly BAK, causing ocular toxicity is controversial. Evidence comparing the same drug entity using BAK versus no preservative or switch studies where patients were switched from a BAK-containing product to PF tafluprost showed some improvement in adverse events; however, results were inconsistent. Tafluprost is an option for those with documented hypersensitivity to BAK or to other PGAs.

**References**

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**Appendix 1: Randomized Controlled Phase 3 Trials**

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| **Study** | **Entry Criteria** | **Intervention** | **Demographic/Baseline data** | **Results** |
| FDA briefing documentsStudy 15-003R, DB, active-control12-monthsN=458Non-inferiority design | **Inclusions**Age ≥18yearsPrimary open-angle glaucoma, pseudoexfoliative glaucoma, pigmentary glaucoma, or ocular hypertensionIOP of 22-34mmHg in at least 1 eye Best corrected ETDRS visual acuity score of +0.6 logMAR or better in each eye**Exclusions**Pregnant females, nursing or planning pregnancy or of child-bearing potential not using a reliable method of birth control; Any uncontrolled systemic disease; h/o of glaucoma filtration surgery; CV, respiratory or ocular surgery within prior 6 months; Change of existing chronic therapy that could affect IOP within 30 days or anticipated change during study; Use of contact lenses; Any active external ocular disease, inflammation or infection of eye or eyelids within 3 months; Any ocular disease that may put the patients at significant risk; Any corneal abnormality or other condition which prevents reliable applanation tonometry; Anterior chamber angle < grade 2; Advanced visual defect; Cannot safely discontinue ocular hypotensive meds during washout; clinically relevant high or low heart rate; contraindications to beta-blockers; h/o retinal detachment, proliferative diabetic retinopathy, or any retinal disease that may progress during study; use of any ocular meds other than anti-glaucoma within 1 week or planned used of other ocular meds during study (intermittent artificial tears allowed); IOP >34mmHg | PC TAF 0.0015% (n=267)PC TIM 0.5% (n=191) | Values for TAF and TIM respectively**Age (yrs):** 61.3; 61.5**Males (%):** 39; 43.5**IOP 8AM (mmHg):** 25.1; 25.6**IOP 10AM (mmHg):** 23.5; 23.8**IOP 4PM (mmHg):** 22.6; 22.7 |

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|  | **Tafluprost** | **Timolol** |
| Completed study (n/N %) | 240/267 (89.9) | 162/191 (84.8) |
| IOP (mmHg)8AM10AM4PM | 18.917.817.7 | 18.517.818.2 |

Non-inferiority was demonstrated |

**Appendix 1-cont.**

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| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Uusitalo 2010Study 74458R, DB, active-control24-monthsN=533ITT analysisNon-inferiority design | **Inclusions**Age ≥18yearsPrimary open-angle glaucoma, capsular glaucoma, pigmentary glaucoma, or ocular hypertension of 22-34mmHg in at least 1 eyeBest corrected ETDRS visual acuity score of +0.6 logMAR or better in each eye**Exclusions**Pregnant females, nursing or planning pregnancy or of child-bearing potential not using a reliable method of birth control; Any uncontrolled systemic disease; Prior filtration surgery or any other ocular surgery within prior 6 months of treated eye(s); IOP≥34mmHg; Change of existing chronic therapy that could affect IOP within 30 days or anticipated change during study; Use of contact lenses; Any active external ocular disease, inflammation or infection of eye or eyelids within 3 months; Any ocular disease that may put the patients at significant risk; Any corneal abnormality or other condition which prevents reliable applanation tonometry; Anterior chamber angle < grade 2; Advanced visual defect; Cannot safely discontinue ocular hypotensive meds during washout; Use of other antiglaucoma meds during study | Washout period according to prior antiglaucoma med.Randomization stratified according to prior PG usePC TAF 0.0015% (n=269)PC LAT 0.005% (n=264)1 drop of medication in affected eye(s) daily at 8pm | Values for TAF and LAT respectively**Age (yrs):** 62.5; 62.4**Female (%):** 59.5; 57.6**Corneal thickness, µm(range):** 554.9 (422-684); 558.5 (432-672)**IOP in worse eye (mmHg):** 24.3±3.0; 23.8±2.8**Prior antiglaucoma meds (%):****PG analog:** 32.7; 32.2**ẞ-blocker:** 29.4; 30.3**PG and ẞ-blocker:** 5.9; 4.5**α-agonist:** 1.1; 1.5**CAI**: 7.8; 4.5 |

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| --- | --- | --- |
|  | **Tafluprost** | **Latanoprost** |
| Completed study at 12 months (n/N %) | 229/269 (85.1) | 247/264 (93.6) |
| Completed study at 24 months (n/N %) | 185/196 (94.4) | 217/224 (96.9) |
| IOP month 24 (mmHg ) | -7.1\* | -7.7  |
| % decrease | 29.1 | 32.2 |
| >0.2 LogMAR score change (%pts) | 11.4 | 14 |
| Corneal thickness (µm) | -10 (OD)-7 (OS) | -7 (OD)-5 (OS) |

\*Treatment difference 0.95 (upper bound CI 1.38). Non-inferiority attained based on treatment difference upper bound 95%CI of <1.5mmHg |
| Chabi 2012Study 001R, DB, active-control12-weeksN=643PP analysisNon-inferiority design | **Inclusions**Age ≥18yearsPrimary open-angle glaucoma, capsular/pseudoexfoliation glaucoma, pigmentary glaucoma, or ocular hypertension Treatment naïve or on stable ocular hypotensive medication at least 30d day priorBest corrected visual acuity score of +0.6 logMAR or better in each eyeIOP 23-36mmHg in at least 1 eyeWilling to avoid wearing contact lenses during study**Exclusions**Any corneal abnormality or other condition which prevents reliable tonometry; Ocular opacity or insufficient dilation preventing retinal evaluation;Narrow anterior chamber angle; Significant visual field defect or progressive visual field loss within last year; Previous use of tafluprost; Inflammatory ocular surface disease; anterior/posterior uveitis (either eye within 6 months), ocular inflammation/infection; progressive retinal disease; significant ocular signs/symptoms; allergic conjunctivitis; history of certain ocular surgeries | Washout period according to prior antiglaucoma med. (dorzolamide rescue allowed if pt.’s IOP was getting too high) Randomization stratified according to IOP <25 or ≥25mmHg and by diagnosis of glaucoma or ocular hypertensionPF TAF 0.0015% (n=320)PF TIM 0.5% (n=323)Doses administered 8AM and 8PM (TAF am dose used vehicle)Both eyes were treated | Values for TAF and TIM respectively**Age (yrs):** 63.3; 63.3**Males (%):** 42.8; 40.6**IOP (mmHg):** 24.9±2.8; 24.7±2.5**IOP <25mmHg (%):** 39.4; 39.3**IOP ≥ 25mmHg (%):** 60.6; 60.7**Open-angle glaucoma (%):** 60.3; 60.1**Ocular hypertension (%):** 39.7; 39.9**Prior PG use (%):** 59.7; 55.1**History of conjunctival hyperemia (%):** 5.9; 5.9**Prior antiglaucoma meds (%):****Bimatoprost:** 12.5; 9.9**Latanoprost:** 36.9; 33.1**Travoprost:** 23.4; 20.7**Timolol**: 9.7; 13**Timolol maleate:** 7.8; 8.7**Brinzolamide:** 11.3; 8.7**Dorzolamide**: 14.7; 14.6 |

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| --- | --- | --- |
|  | **Tafluprost** | **Timolol** |
| Completed study (n/N %) | 306/320 (95.6) | 312/323 (96.6) |
| d/c due to AE (n) | 4 | 3 |
| PP pop analyzed for efficacy (n) | 299 | 313 |
| IOP (mmHg)\* | -6.9 [-7.2, -6.6] | -6.6 [-6.9, -6.3] |
| ≥25% ↓ in IOP (% pts) | 59.7 | 49.7 |

\*Treatment difference -0.3 [-0.7, 0.1]. Non-inferiority attained based on treatment difference upper bound 95%CI of <1.5mmHg |
| Egorov 2009Study 74460R, DB12-weeks (6-week + 6-week extension)N=185ITT analysisSuperiority trial | **Inclusions**Age ≥18yearsPrimary open-angle glaucoma, capsular/pseudoexfoliation glaucoma, pigmentary glaucoma, or ocular hypertension PG treatment naïveBest corrected visual acuity score of +0.6 logMAR or better in each eyeIOP of 22-30mmHg after a 4-week run-in period with timolol**Exclusions**Pregnant or likely to become pregnant; any uncontrolled systemic disease; contraindications to beta-blockers; contact lens use; any disease or abnormality of the external part of the eye; anterior chamber angle <2; advanced or progressive visual field defect; anticipated use of another glaucoma med during study | 4-week run-in with TIM6-weeksPC TAF 0.0015% + PC TIM 0.5% (n=96)Vehicle + PC TIM 0.5% (n=89)TIM administered at 8am and 8pmTAF or vehicle administered at 8:10pm6-week extensionAll patients received TAF + TIM | Values for TAF and vehicle respectively**Age (yrs):** 66.3; 68.0**Females (%):** 59.4; 52.8**IOP 8AM (mmHg):** 24.6; 24.6**IOP 10AM (mmHg):** 23.8; 23.6**IOP 4PM (mmHg):** 23.1; 23.3 |

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| --- | --- | --- |
|  | **Tafluprost** | **Vehicle** |
| Completed randomized period(n/N %) | 90/96 (93.8) | 85/89 (95.5) |
| Completed extension phase (n/N %) | 89/90 (98.9) | 82/85 (96.5) |
| IOP (mmHg) week 68am10am4pm | -5.49\*-5.82\*-5.53\* | -4.01-3.99-4.15 |
| IOP (mmHg) week12ⱡ8am10am4pm | -6.79-6.75-6.22 | -6.72-6.44-6.12 |

ⱡ the TAF arm received TAF for 12 weeks; the vehicle arm received vehicle for 6 weeks then TAF for 6 weeks\*significant vs. vehicle |

**Appendix 1-cont.**

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| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Hamacher 2008R, investigator-masked, CO4 weeks/ armN=43ITT analysis | **Inclusions**Age ≥18yearsPrimary open-angle glaucoma, capsular glaucoma, pigmentary glaucoma, or ocular hypertension Prior PGA use with ≥15% decrease in IOPIOP 22-34mmHg after washoutBest corrected visual acuity score of +0.6 logMAR or better in each eye**Exclusions**IOP >34; known allergy/hypersensitivity to study meds; use of contact lenses at screening or during study; prior filtration surgery or other ocular surgical procedures in past 6 months; any condition preventing reliable applanation tonometry; advanced visual field defect, active external ocular disease; inflammation or infection of the eye or eyelids within 3 months; ocular presence of any uncontrolled systemic disease; pregnant or breastfeeding | Washout according to prior glaucoma medsPC TAF 0.0015%PF TAF 0.0015%TAF administered once daily at 8pmPatients treated for 4 weeks then switched to other arm after washout of at least 4 weeks | **Age (yrs):** 65.3**Females (%):** 62.8**Open-angle glaucoma (%):** ~60**Ocular hypertension (%):** ~30**Corneal thickness (µm)**Right eye: 548.7Left eye: 547.0 |

|  |  |
| --- | --- |
|  | **Tx difference PF TAF – PC TAF [95%CI]** |
| IOP at week 4 8am12pm4pm8pm | 0.24 [-0.51, 0.98]0.11 [-0.64, 0.86]0.00 [-0.74, 0.75]-0.30 [-1.04, 0.45] |

Product equivalency was established |

**Appendix 2: Switch studies**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Study** | **Entry Criteria** | **Intervention** | **Demographic/Baseline data** | **Results** |
| Uusitalo 2010Open-label; all patients switched12-weeksN=158 | **Inclusions**Primary open-angle glaucoma, capsular glaucoma or ocular hypertensionTx with latanoprost ≥ 6months≥ 2 ocular symptoms OR 1 symptom AND 1 sign of ocular surface irritation/inflammationⱡ**Exclusions**Pigmentary or closed-angle glaucoma; IOP >22mmHg during lantanoprost tx; glaucoma filtration surgery or any other ocular surgery within past 6 months; use of artificial tears containing preservatives; contact lens use; corneal abnormalities affecting tonometry; pregnant/nursingⱡIrritation/burning/stinging; foreign body sensation; tearing, itching, or dry eye sensation graded at least as mild; fluorescein breakup time <10 sec; corneal fluorescein staining score corresponding to at least grade1 (Oxford Grading Scale) and/or combined nasal and temporal conjunctival staining score of at least grad II, blepharitis or conjunctiva hyperemia of at least mild severity or tear production ≤ 10mm in Schirmer’s test | Latanoprost→tafluprost PFIOP, symptoms and signs, cytology evaluated by an independent observerResults of the worse eye was used for the analyses | **Age (yrs):** 68.9**Females (%):** 65.8**Duration of latanoprost (yrs):** 3.3 [0.4, 12.7]  |

|  |  |  |
| --- | --- | --- |
|  | **Latanoprost** | **Tafluprost PF** |
| IOP (mmHg) | 16.8±2.5 | 16.4±2.7\* |
| fTBUT (s) | 4.5±2.5 | 7.8±4.9\* |
| HLA-DR pos.§(% cells) | 61.2±11.5 | 52±22.9\* |
| MUC5AC (% cells)§ | 3.8±1.4 | 6.7±3.1\* |

\*significant vs. latanoprost§based on patients expressing abnormal values at baseline

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **None** | **Trace** | **Mild** | **Mod** | **Severe** |
| **Inflammation/ burning/stinging**Baseline12 weeks | 5093 | 1918 | 4923 | 2721 | 130 |
| **Tearing (n)**Baseline12 weeks | 5384 | 1829 | 3628 | 3111 | 203 |
| **Foreign body sensation (n)**Baseline12 weeks | 6299 | 1814 | 3626 | 3114 | 112 |
| **Itching (n)**Baseline12 weeks | 6880 | 1634 | 4127 | 2512 | 82 |
| **Dry eyes (n)**Baseline12 weeks | 4180 | 1514 | 4141 | 4118 | 202 |
| **Blepharitis (n)**Baseline12 weeks | 6392 | -- | 8161 | 132 | 10 |

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Oxford scale** | **0** | **I** | **II** | **III** | **IV** | **V** |
| **Corneal staining (n)**Baseline12 weeks | 2992 | 6847 | 5015 | 101 | 10 | 00 |

Oxford scale (0-V): higher number indicates greater severity |

**Appendix 2- cont.**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Ranno 2012All patients switched3 monthsN=91 (89 included in analysis: 2 were lost to f/u) | **Inclusions**≥18 years oldPrimary open-angle glaucoma, Monotx with lantoprost, travoprost, bimatoprost ≥ 3monthsComplaining of ocular surface discomfortIOP <21mmHg**Exclusions**Barely open anterior chamber angle, h/o acute angle closure ocular trauma, h/o ocular surgery, argon laser trabeculoplasty, ocular inflammation or infection within past 3 months, neovascular glaucoma, h/o refractive surgery | Latanoprost, bimatoprost, travoprost→ tafluprost PF(no washout period between prior PGA and tafluprost PF)IOP and tolerability was assessed by a masked operator | **Age (yrs):** 64.7**Latanoprost (n):** 29**Travoprost (n):** 28**Bimatoprost (n):**32 |

|  |  |  |
| --- | --- | --- |
|  | **Baseline PGAs** | **Tafluprost PF** |
| IOP (mmHg) | 16±2.1 | 16.6±2.0 |
| **IOP by PGA**LatanoprostTravoprostBimataprost | 16.5±2.315.9±2.515.6±1.8\* | 16.6±2.016.6±2.016.6±2.0 |
| Conjunctival hyperemia | 1.2±o.8 | 1.0±0.6 |
| **Conjunctival hyperemia by PGA**LatanoprostTravoprostBimataprost | No diffNo diff1.3±0.9\* | --1.0±0.6 |
| Punctuate keratitis  | 0.8±0.6 | 0.8±0.6 |
| **Punctuate keratitis by PGA**LatanoprostTravoprostBimataprost | No diffNo diff0.9±0.7\* | --0.7±0.6 |
| Ocular discomfort | 75% of pts had Improvement, 21% unchanged, 4% worsening |

\*Significant vs. tafluprost |
| Januleviciene 2012All patients switched12 weeksN=30 pts (60 eyes) | **Inclusions**≥18 years oldopen-angle glaucoma ± pseudoexfoliation or pigment dispersion componentBest corrected visual acuity 20/40 or betterAt least mild dry eye (OSDI or corneal fluorescein staining)Monotx with lantoprost, ≥ 1monthIOP controlled**Exclusions**Any abnormality preventing reliable applanation tonometry; treatment of dry eye with punctal plugs, punctal cautery, cyclosporine, topical ocular steroids, artificial tear that have not been d/c’d; keratorefarctive ocular laser procedure; corenal surgery or surgery to corneal suface within 1 year; intraocular or extraocular surgery within 6 months; progressive retinal or optic nerve disease; severe central visual field loss; any h/o infectious or inflammatory ocular conditions; ocular trauma within 6 months; unstable dosing regimen of any chronic systemic meds | Latanoprost→tafluprost PF | **Age (yrs):** 64.2**Females (%):** 86.7**Duration of latanoprost (yrs):** 3.3 [0.4, 12.7]**IOP (mmHg):** 16.2±2.4 |

|  |  |  |
| --- | --- | --- |
|  | **Latanoprost** | **Tafluprost PF** |
| Tear osmolality (mOsm/L) | 315.7±15.1 | 302 ±9.9\* |
| ↓ tear osmolality (% of eyes)ⱡ | - | 81.7 |
| TBUT (sec) | 3.7±1.1 | 6.5±1.5 |
| Abnormal fluorescein staining (% of eyes) | 75 | 11.7 |
| IOP (mmHg) | 16.4±3.0 | 16.3±2.3 |
| Dry eye complaints (% pts) ⱡ | 100 | 36.7\* |

 ⱡn=60 eyes |
| Hommer 2011Non-interventional, observational, open-label, non-randomized12 weeksN=118 | Patients with glaucoma or ocular hypertension with tolerability issues and insufficient IOP control with prior medical therapy | Prior PGA→tafluprost PFSwitch done at provider discretion Participating ophthalmologists provided anonymous pt. data using standardized data collection format.  | **Age (yrs):** 63.6**Females (%):** 69.5**Duration of glaucoma (yrs):** 6.7 [1-22]**IOP (mmHg):** 16.2±4.3**Prior monotx with PGA (%)****Latanoprost**: 57.6**Travoprost:** 27.1**Bimatoprost:** 15.3**Reasons for switch****Ocular symptoms (%pts):** 61.0**Insufficient IOP decrease (% pts):** 20.3**Systemic intolerability (%):** 5.1 |

|  |  |  |
| --- | --- | --- |
|  | **Prior PGA** | **Tafluprost PF** |
| IOP (mmHg) | 16.2±4.3 | 14.8±3.2 |
| **IOP by PGA**LatanoprostTravoprostBimataprost | 16.2±4.616.2±4.316.4±3.5 | 14.8±3.114.9±3.315.0±3.3 |
| No signs of hyperemia (%pts) | 35.6 | 87.7 |
| Burning (%pts) | 55.9 | >90% of patients had improvement with each of the symptoms. The remainder had no change and none had worsening |
| Foreign body sensation (%pts) | 36.5 |
| Itching (%pts) | 33.1 |
| Irritation (%pts) | 58.5 |
| Stinging (%pts) | 16.9 |
| Tearing (%pts) | 27.1 |
| Dryness (%pts) | 21.2 |
| Discontinued Tafluprost PF (n) | - | 12\*\* |

\*\*3 lack of efficacy; 2 conjunctival hyperemia; 3 handling issues and preference; 3 tolerability issues (burning/stinging, hyperemia, dryness); 1 subjective malaise |

**Appendix 3: Reported Adverse Events in Randomized Clinical Trials (%)**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **Study 15-003** | **Uusitalol 2010** | **Chabi 2012** | **Egorov 2009** | **Hamacher 2008** |
| **Tafluprost PC****N=267** | **Timolol PC****N=191** | **Tafluprost PC****N=264** | **Latanoprost PC n=264** | **Tafluprost PF****N=320** | **Timolol PF****N=323** | **Tafluprost + Timolol PC****N=96** | **Vehicle + Timolol PC****N=89** | **Tafluprost PC****N=42** | **Tafluprost PF****N=43** |
| Eyelash growth |  |  | 6.4 | 4.2 |  |  | 1.0 | 1.1 | 4.8 | 13.9 |
| Eye irritation |  |  | 5.3 | 5.3 | 0.9 | 1.2 | 3.1 | 1.1 |  |  |
| Eyelash discoloration |  |  | 4.8 | 3.8 |  |  |  |  |  |  |
| Eye pain |  |  | 5.6 | 2.7 |  |  | 3.1 | 0 | 0 | 2.3 |
| Ocular hyperemia | 12.7 | 5.2 | 5.3 | 2.7 | 1.6 | 0.6 |  |  | 0 | 4.7 |
| Cataract |  |  | 3.0 | 3.8 |  |  |  |  |  |  |
| Conjunctival hyperemia |  |  | 4.2 | 1.5 | 2.8 | 0 | 14.6 | 9.0 |  |  |
| Dry eyes |  |  | 2.7 | 1.9 | 0.9 | 1.2 | 2.1 | 0 |  |  |
| Eye pruritus | 7.1 | 2.6 | 2.3 | 1.1 | 1.9 | 0.9 | 14.6 | 0 | 2.4 | 2.3 |
| Eyelash thickening |  |  | 1.9 | 1.5 |  |  |  |  |  |  |
| Eyelid edema |  |  | 1.9 | 1.5 |  |  | 2.1 | 1.1 | 2.4 | 2.3 |
| Iris hyperpigmentation |  |  | 1.5 | 1.5 |  |  |  |  |  |  |
| Visual field defect |  |  | 1.9 | 1.1 |  |  | 0 | 1.1 |  |  |
| Foreign-body sensation |  |  |  |  |  |  |  |  | 2.4 | 2.3 |
| Conjunctivitis allergic |  |  |  |  |  |  | 2.1 | 0 |  |  |
| Blurred vision |  |  |  |  | 0.6 | 1.9 | 1.0 | 0 | 2.4 | 0 |
| Photophobia |  |  |  |  | 1.3 | 0 |  |  |  |  |