

**Brand Name:** Zioptan

**Generic Name:** tafluprost

**Manufacturer**<sup>1,2</sup>: Merck Sharp & Dohme Corp., a Subsidiary of Merck & Co., Inc.

**Drug Class**<sup>1,2,3,4</sup>: Antiglaucoma, Prostaglandin analog

**Uses:**

**Labeled Uses**<sup>1,2,3,4</sup>: Reduction of intraocular pressure (IOP) in adults with ocular hypertension or open-angle glaucoma.

**Unlabeled Uses**<sup>1,2,3,4</sup>: None

**Mechanism of Action**<sup>1,2,4</sup>: Tafluprost is a prostaglandin analog that acts as a selective agonist at the fluoroprostaglandin prostanoid receptor. The exact mechanism of action is unknown. It is believed to reduce intraocular pressure by increasing uveoscleral outflow.

**Pharmacokinetics**<sup>1,2,3,4</sup>:

**Absorption:** After ocular administration, tafluprost is absorbed through the cornea. After administration of one drop of tafluprost 0.0015%, peak plasma concentrations of tafluprost acid are achieved within 10 minutes. Reduction of intraocular pressure begins approximately 2 to 4 hours after the first dose and the maximum effect is achieved within 12 hours. The mean plasma  $C_{max}$  was 26 pg/mL on day 1 and 27 pg/mL on day 8. The mean plasma AUC was 394 pg\*min/mL on day 1 and 432 pg\*min/mL on day 8.

**Metabolism:** Tafluprost is an ester pro-drug that is hydrolyzed to its biologically active metabolite, tafluprost acid, in the eye. The acid metabolite is further metabolized by fatty  $\beta$ -oxidation and phase II conjugation.

**Elimination:** Because tafluprost has minimal systemic absorption, the mechanism of elimination is unclear.

**Efficacy:**

**Schnober D, Hofmann G, Maier H, Scherzer ML, Ogundele A, and Jasek M. Diurnal IOP-lowering efficacy and safety of travoprost 0.004% compared with tafluprost 0.0015% in patients with primary open-angle glaucoma or ocular hypertension. Clin Ophthalmol. 2010; 4; 1459-1463.**

**Study Design:** Randomized, double-blind, active comparator, cross-over design

**Description of Study:** *Methods:* Fifty-one patients with a clinical diagnosis of primary open-angle glaucoma or ocular hypertension in at least one eye were randomized to receive either travoprost ophthalmic solution 0.004% or tafluprost 0.0015% for the first six weeks, after which the first study medication was discontinued and the other study medication was initiated and continued for another six weeks. Measures conducted at the week 6 and week 12 visits included a solicited symptom survey, bilateral IOP diurnal curve, bilateral best-corrected Snellen visual acuity (BCVA), hyperemia assessment, and bilateral slit-lamp biomicroscopy. Adverse events were collected, monitored, and evaluated throughout the study. *Outcome Results:* The 12-hour mean diurnal IOP was statistically significantly lower with travoprost than with tafluprost ( $p = 0.01$ ). A statistically significant lower IOP was also reported for travoprost at five of the seven time points including 8 p.m. which was the primary endpoint of the study. Both medications produced a similar pattern of IOP control with peak IOP reductions observed 12 hours after dosing and trough reductions observed 20 hours after dosing. Neither medication produced a statistically significant increase from baseline in any of the individual symptom scores except for hyperemia which revealed a statistically significant increase in both groups ( $p=0.01$  and  $<0.01$ ). No treatment-related adverse events were reported.

**Limitations:** It is not known if the patient's were on a prostaglandin analog that was ineffective prior to the study, likely making travoprost or tafluprost ineffective as well. Participants were provided with instructions for using their eye drop, but proper administration of an eye drop was not assessed. In addition, compliance was not addressed. The study utilized a cross-over design with no wash-out period between switching medications. Lastly, one of the most concerning side effects of prostaglandin analogs is hyperpigmentation with chronic administration; due to the short duration of this study, long term effects of these medications cannot be compared.

**Conclusion:** Although travoprost produced a statistically significant lower mean IOP, the actual difference in IOP's was small (0.4 – 0.7 mmHg). The clinical significance of such a small difference is unclear. Further study is needed with a longer duration in order to determine and compare long-term adverse effects of these medications.

**Chabi A, Varma R, Tsai J, Lupinacci R, Pigeon J, Baranak C, et al. Randomized clinical trial of the efficacy and safety of preservative-free tafluprost and timolol in patients with open-angle glaucoma or ocular hypertension. Am J Ophthalmol. 2012: doi: 10.1016/j.ajo.2011.11.008**

**Study Design:** Phase III, multicenter, randomized, double-blind, active comparator, parallel-group design

**Description of Study:** *Methods:* Six hundred and forty-three patients with a diagnosis of primary open-angle glaucoma, pigmentary glaucoma, capsular glaucoma/pseudoexfoliation, or ocular hypertension were randomized to receive preservative-free (PF) tafluprost 0.0015% or PF timolol maleate 0.5%. Patients randomized to timolol received unit dose pouches marked for morning and evening administration; patients randomized to tafluprost received PF vehicle in the morning pouches and tafluprost in the evening pouches. Investigators were allowed to administer dorzolamide if they felt the patient's IOP was getting too high during the wash-out period. Efficacy was assessed by IOP measurements at baseline, and at week 2, 6, and 12. Safety was assessed by ocular assessments and vital signs. While masked, investigators determined severity, seriousness, and likelihood of adverse events with the study drug. Compliance was assessed by a dosing diary and counting study medication at each visit. The primary outcome measure was mean IOP change from baseline at weeks 2, 6, and 12. A secondary outcome measure was the proportion of patients with a favorable IOP response. An additional outcome measure was the mean change from baseline in diurnal IOP at weeks 2, 6, and 12. *Outcome Results:* There was a statistically significant difference between the IOP change from baseline in patients receiving tafluprost and timolol during week 2 at 10:00 and 16:00 (95% CI -1.1, -0.3, and -1.3, -0.4 respectively), week 6 at 16:00 (95% CI -1.3, -0.3), and week 12 at 16:00 (95% CI -1.0, -0.1). There was no statistically significant difference in the percentage of patients with  $\geq 25\%$  reduction in diurnal IOP from baseline at week 2, 6, or 12 (95% CI -1.8, 14.1; -1.7, 14.0; -3.6, 12.1 respectively). There was a statistically significant difference in mean change from baseline in diurnal IOP only at week 2 (95% CI -1.1, -0.3) and 6 (95% CI -0.8, -0.004). Adverse events were reported with a similar incidence in both treatment groups (22.8% and 22.6% of patients in the tafluprost and timolol groups, respectively).

**Limitations:** A potential conflict of interest exists because the Scientific Advisory Committee included Merck scientists and they contributed to the development of the protocol, statistical analysis plan, analysis and interpretation of the data, and authoring of the manuscript; Merck manufactures tafluprost. Twelve weeks is not a sufficient duration to evaluate the incidence of long-term side effects of prostaglandin analogs on iris pigmentation.

**Conclusion:** This study showed that PF tafluprost and PF timolol have a substantial IOP-lowering effect. The IOP-lowering effect of tafluprost was noninferior to that of timolol at all visits and time points over 12 weeks. The PF formulation of tafluprost achieves good diurnal control of IOP and is well tolerated, which may be of particular value in

patients allergic to preservatives or have adverse events related to preservative-containing ocular hypotensives.

**Uusitalo H, Pillunat L, Ropo A. Efficacy and safety of tafluprost 0.0015% versus latanoprost 0.005% eye drops in open-angle glaucoma and ocular hypertension: 24-month results of a randomized, double-masked phase III study. Acta Ophthalmol. 2010; 88; 12-19.**

**Study Design:** Phase III, multicenter, randomized, double-blind, active comparator, parallel-group design

**Description of Study:** *Methods:* Five hundred and thirty-three patients with open-angle glaucoma or ocular hypertension were randomized to receive tafluprost 0.0015% or latanoprost 0.005% once daily for 24 months. In addition to the baseline visit, study visits occurred after 2 weeks and 6 weeks, as well as 3, 6, 9, 12, 12.5-13, 15, 18, and 24 months. During these visits, patients were assessed for changes to prior and concomitant medications, adverse events, visual acuity, biomicroscopy, conjunctival redness, IOP, and compliance. Photographs were taken of eyes and lids for comparison with baseline photographs. The primary efficacy endpoint was change from baseline in the overall diurnal IOP. Diurnal IOP was based on recordings taken at 8:00, 12:00, 16:00, and 20:00. Safety and tolerability measures included adverse events, ocular safety, overall drop discomfort, systemic (blood pressure and heart rate) and laboratory safety variables. *Outcome Results:* At 24 months, the mean decrease in diurnal IOP from baseline was -7.1 mmHg in the tafluprost group and -7.7 mmHg in the latanoprost group. Amongst prostaglandin naïve patients, there were slightly more cases of severe iris pigmentation in the latanoprost group, but overall the difference in iris pigmentation between groups at month 24 was not statistically significant ( $p=0.848$ ).

**Limitations:** More patients in the tafluprost group had been using prostaglandin analogs and  $\beta$ -blockers prior to enrollment in the study. This suggests that there were more treatment-resistant patients in this group, which may have been reflected by the higher baseline IOP. Another limitation of this study is the way the results were presented. Results were presented in bar graph format, so it's hard to determine the actual numerical values.

**Conclusion:** Tafluprost and latanoprost both have substantial IOP lowering effects that were sustained for the 24 month period. Adverse events were similar between groups. It is important to note that both medications administered in this study contained preservatives, which have been shown to cause numerous adverse effects to the ocular surface. A preservative free formulation of tafluprost is available and studies have demonstrated equivalent pharmacokinetics and efficacy to the preservative

counterpart. Tafluprost is noninferior to latanoprost and can be considered an option for the treatment of patients with open-angle glaucoma or ocular hypertension.

**Contraindications**<sup>1,2,3,4</sup>: None

**Precautions**<sup>1,2,3,4</sup>:

**Pigmentation**: Pigmentation of the iris, periorbital tissue, and eyelashes can occur. Pigmentation of the iris is likely to be permanent.

**Eyelash Changes**: Gradual changes to the eyelashes can occur such as increased length, thickness, and number of lashes which is usually reversible.

**Intraocular Inflammation** (iritis/uveitis): Use with caution in patients with active intraocular inflammation because the inflammation may be exacerbated.

**Macular Edema**: Macular edema has been reported during treatment with prostaglandin F<sub>2α</sub> analogs. Use with caution in aphakic patients, in pseudophakic patients with a torn posterior lens capsule, or in patients with known risk factors for macular edema.

**Pediatric Use**: Use in pediatric patients is not recommended due to possible safety issues of increased pigmentation following long-term use. Safety and efficacy has not been established in neonates, infants, children, and adolescents.

**Adverse Effects**<sup>1,2,3,4</sup>:

Ocular:

- Conjunctival hyperemia (4% to 20%)
- Ocular irritation/stinging (7%)
- Ocular pruritus (including allergic conjunctivitis) (5%)
- Cataracts (3%)
- Dry eye (3%)
- Ocular pain (3%)
- Blurred vision (2%)
- Eyelash darkening and growth (2%)

Other:

- Headache (6%)
- Common cold (4%)

Cough (3%)

Urinary tract infection (2%)

**Drug Interactions**<sup>1,3</sup>: Drug-drug interactions are not expected. Tafluprost can be used concomitantly with other ophthalmic medications used to decrease intraocular pressure. If more ophthalmic preparations are used, administer each one at least 5 minutes apart.

**Dosing/Administration**<sup>1,2,3,4</sup>:

*Adult and Geriatric Dosing*

Instill 1 drop in the conjunctival sac of the affected eye(s) once daily in the evening. More frequent administration may decrease the intraocular pressure lowering effect.

*Pediatric Dosing*

Safety and efficacy has not been established.

*Hepatic and Renal Impairment Dosing*

Specific guidelines are not available; it appears that no dosage adjustments are necessary.

**Use in Special Circumstances**<sup>1,2,3,4</sup>:

*Pregnancy*

Tafluprost is a pregnancy category C drug. There are no adequate and well-controlled studies of tafluprost in pregnant women. According to the manufacturer, tafluprost should not be administered during pregnancy unless the potential benefit outweighs the potential risk to the fetus.

*Breastfeeding*

It is not known whether tafluprost is excreted in human milk. Due to minimal systemic absorption after ophthalmic administration, clinically significant amounts of the drug are not expected to be bioavailable to a nursing infant from breastmilk. According to the manufacturer, caution should be exercised when administered to a breast-feeding woman.

**Conclusion:** Tafluprost shows comparable efficacy and safety to other prostaglandin analogs including travoprost and latanoprost. There is also comparable efficacy and safety with the  $\beta$ -blocker timolol, although it is important to remember timolol must be administered twice daily and tafluprost is only administered once daily which may impact patient compliance. The monthly cost of tafluprost is higher compared to latanoprost but more cost effective than travoprost. A preservative free formulation of tafluprost is available and should be considered

in patients who have experienced preservative-related adverse reactions to latanoprost and travoprost. If a prostaglandin analog is deemed necessary, tafluprost 0.0015% is an appropriate recommendation for the treatment of patients with open-angle glaucoma or ocular hypertension.

**Recommended References:**

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4. Tafluprost. In: DRUGDEX® System [Internet Database]. Thomson Reuters, 2012. Updated periodically. Available at: <http://www.micromedex.com> Accessed: April 5, 2012.
5. Sutton A, Gilvarry A, Ropo A. A comparative, placebo-controlled study of prostanoid fluoroprostaglandin-receptor agonists tafluprost and latanoprost in healthy males. *Journal of Ocular Pharmacology and Therapeutics*. 2007; 23(4); 359-365.
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