Abstract: The fixed combination eye drop Duotav is a combination of travoprost 0.004% and timolol maleate 0.5%. Both travoprost and timolol have been used separately for the treatment of glaucoma by lowering intraocular pressure. Multiple studies have demonstrated the efficacy and safety of the fixed combination travoprost/timolol for the treatment of open-angle glaucoma and ocular hypertension. The once daily dosing of this combination offers multiple potential advantages such as patient adherence, potential cost advantages, and reduction in exposure to preservatives. This article discusses the benefits of fixed combination medications and summarizes past and recent studies listed on the online resource PubMed of the fixed combination travoprost/timolol with comparison to both monotherapy and other similar fixed combination ocular hypotensive preparations.

Keywords: fixed combination, travoprost, travatan, timolol, glaucoma, DuoTrav
Introduction
The latest estimate projects that by the year 2010 there will be 60.5 million people affected with glaucoma.\(^1\) This same study projected this number to reach 79.6 million by the year 2020.\(^1\) Glaucoma remains the number two cause of blindness in the world based on the World Health Organization study in 2004.\(^2\) Research studies have shown a relationship between elevated intraocular pressure and the increased risk of visual field loss.\(^3\) The only proven modifiable risk factor for preventing the progression of glaucoma is intraocular pressure (IOP) reduction. Numerous multicenter, randomized, prospective trials have validated the efficacy of IOP reduction in preventing optic nerve damage, visual acuity loss, and visual field loss.\(^4\)–\(^7\) Long term follow up of the patients in these studies have reinforced the original findings that IOP reduction does prevent glaucomatous visual field loss.\(^8\)–\(^9\)

Intraocular pressure reduction can be achieved by surgical or medical means. The surgical spectrum includes laser treatments to the trabecular meshwork or ciliary body and incisional techniques. Laser treatment has been validated in large clinical trials such as the Glaucoma Laser Trial to be as effective as medical treatment in controlling IOP.\(^10\) Laser modalities such as Selective Laser Trabeculoplasty (SLT) offer the advantage of repeatability.\(^11\) Newer laser treatments such as endoscopic cyclophotocoagulation (ECP) are being combined with cataract surgery to lower IOP.\(^12\),\(^13\) Although laser surgery is an effective treatment for many types of glaucoma, its effects can be ephemeral or contraindicated in some forms of glaucoma. Incisional surgery includes a variety of methods such as trabeculectomy, glaucoma drainage devices, ab interno trabeculectomy, and viscocanalostomy.

Incisional techniques have been validated and compared to medical treatment in large multicenter trials with some shown to be equivalent.\(^14\) Not all patients are candidates for incisional surgery. Many of the surgical techniques profiles are unacceptable to patients for one or multiple reasons including: various techniques cannot be performed due to anatomical variability, surgery may require extensive lifestyle modifications, additional office visits, and cannot guarantee patients they will be relieved of medication use entirely.

Medical therapy for glaucoma remains the mainstay of initial and long term IOP reduction. Topical and systemic IOP reducing drugs are both available. The systemic medications include carbonic anhydrase inhibitors and hyperosmotics. The array of topical medications has changed throughout the years, as has the mechanism of action of these medications. The current topical medications include β-adrenergic antagonists, α-adrenergic agonists, prostaglandin analogs, carbonic anhydrase inhibitors, and miotics. Topical medications have numerous studies to support their efficacy in IOP reduction. These medications are available from multiple manufactures in both generic and non-generic preparations, in various concentrations, utilize a variety of preservatives, some available in combination preparations.

Recommended dosage of the medications is variable. Depending on the medication, it can be administered in the morning or evening, one to four times per day. Clinicians choose a particular medication based on the mechanism of IOP elevation, safety profile of the medication, and other factors that pertain to the individual patient such as medical history. After a particular medication is chosen and therapy initiated, the IOP is reevaluated to determine the effects of the medication. The IOP levels in some patients may require a drastic reduction, in some cases 50%, or more. Many patients require mono-therapy to achieve adequate IOP reduction. Once a day therapy, effectiveness, and a relatively safe profile has made prostaglandin analogs the de facto first-line therapy for glaucoma and ocular hypertension.

Unfortunately, many patients require multiple medications to lower the IOP to levels required to prevent further optic nerve damage. The addition of a second medication to a treatment regimen creates new barriers to medication compliance including financial, administration, and tolerance issues. The lack of compliance to ophthalmic medications is nothing new to ophthalmology.\(^15\),\(^16\) Studies have shown that compliance is further reduced with the addition of a second topical glaucoma medication.\(^17\) Recently, combination preparations have been made available for IOP reduction.\(^18\),\(^19\) The use of a fixed combination medication (FCM) has been around for many years.\(^20\)–\(^22\) Numerous studies
have validated the efficacy and compliance of these combinations in multiple disease states.\textsuperscript{23–26} The majority of published studies on FCM show improved compliance and efficacy of the class of medications.

This article will discuss the IOP reducing FCM travoprost-timolol and provide a current review of pharmacology, efficacy studies, safety, and thoughts on therapeutic uses.

Introduction to Travoprost-Timolol

The FCM travoprost-timolol, marketed as Duotrat (Alcon Pharmaceuticals), is a combination of the ophthalmic solutions travoprost 0.004% and timolol 0.5%. Duotrat is preserved with 0.015% benzalkonium chloride.\textsuperscript{18} Currently, Duotrat is not available in the United States.

Travoprost 0.004% (Travatan, Alcon Pharmaceuticals) was approved for IOP reduction in the United States in 2001.\textsuperscript{27} It has been proven effective in IOP reduction as both monotherapy and combination therapy.\textsuperscript{28–30} Travoprost is a selective F\textsubscript{2α} (FP) prostaglandin receptor agonist and is the isopropyl ester of the positive enantiomer of fluprostenol (a selective FP prostanoid receptor agonist).\textsuperscript{31} After being absorbed by the cornea, the prodrug is hydrolyzed by corneal esterases forming the active free acid AL-5848. One of the hydrolyzed chains, the \(\omega\) chain, is responsible for both the selectivity and potency of the drug once in the eye.

The exact mechanism of IOP reduction of travoprost and other prostaglandin analogs is not fully understood. Studies are mixed and suggest that the IOP reduction is due to increased pressure independent or unconventional (uveoscleral) outflow and/or increased pressure dependent or conventional (trabecular meshwork) outflow, the former being the favored theory. The two mechanisms studied to explain prostaglandin analogs effect on uveoscleral outflow are relaxation of the ciliary muscle and/or remodeling of the extracellular matrix of the ciliary muscle. Studies are conflicting that explain the ciliary muscle relaxation theory.\textsuperscript{32,33}

Most evidence supports re-modeling of the extracellular matrix in the ciliary muscle.\textsuperscript{34} The remodeling mechanism involves activation of the FP receptor to initiate a complex transduction cascade. The cascade leads to activation of various nuclear transcription factors, matrix metalloproteinases and other pro-enzymes. These pro-enzymes are believed to be responsible for degradation of extracellular matrix substrates including collagen, fibronectin, and/or laminin.\textsuperscript{35}

A recent study in healthy normal volunteers reported three available prostaglandin analogs; bimatoprost, latanoprost, and travoprost’s mechanism of action occurs at the conventional or unconventional pathways, depending on the type of measurement utilized.\textsuperscript{36} The authors feel the results of this study may explain conflicting reports on the mechanism of action of prostaglandin analogs. In this study one of the prostaglandin analogs (travoprost, bimatoprost, latanoprost), or placebo was administered to one eye daily of 30 patients. The IOP was measured with Shiotz tonography and pneumonatography. Fluorophotometry was used to measure aqueous humor flow rate and fluorophotometric outflow facility. The Goldmann equation was used to measure outflow facility and uveoscleral outflow was calculated from aqueous humor flow rate. The study revealed that both (conventional/unconventional) of the outflow pathways contribute to IOP reduction, depending on which measurement was performed. A previous study corroborates these findings with travoprost.\textsuperscript{37}

Once a day dosing of travoprost 0.004% has been shown to decrease IOP from baseline 30%–33% and a baseline IOP reduction ranging from \(-6.5\) to \(-8.0\) mmHg.\textsuperscript{29,30} The plasma half-life of travoprost is 45 minutes. An IOP reduction is detectable at two hours post dose and peaks at \(-12\) hours. Travoprost has not been shown to affect the blood chemistry of patients with renal or hepatic impairment. It is listed as a category C for pregnant and breastfeeding mothers.

The side effects of the prostaglandin analogs include ocular irritation, conjunctival hyperemia, increased pigmentation of the pericircular skin and iris, and hypertrichosis of the eyelashes. The hyperpigmentation of the skin is due to increased melanosomes (pigment granules) in melanocytes and not increased numbers of melanocytes. Hypertrichosis occurs from prostaglandin analog use secondary to changes in the hair follicle cell cycle. Travoprost is relatively contraindicated in patients with a history of uveitis and/or risk factors for cystoid macular edema.
especially aphakic or pseudophakic patients with torn posterior capsules.

Timolol was the first topical β-receptor antagonist available for the treatment of glaucoma. Timolol maleate is a nonselective β-adrenergic receptor antagonist with affinity for both β-1 and β-2 adrenergic receptors used for IOP reduction. Topical propranolol, a non-selective β-receptor antagonist, was the first β-receptor antagonist found to lower IOP with topical administration. Formulations of selective β-1 antagonists are available and often used in patients with pulmonary disease. Timolol is available in two concentrations, 0.25% and 0.5%. A viscous gel formulation is available and used to aide adsorption (XE type). Timolol is typically dosed twice daily. Studies have shown equivalence in daily dosing with the gel formulation compared to twice a day dosing with the liquid formulation timolol.

Timolol maleate is moderately (∼60%) bound by plasma proteins and enters the eye primarily through the cornea. Blockage of the β-1 and β-2 receptors, both G-protein linked, by timolol results in decreased production of aqueous humor by the non-pigmented epithelium of the ciliary body. The process or aqueous humor formation is not fully understood but involves the activation of adenyl cyclase, formation of cAMP, and aqueous formation in the ciliary body. Studies have shown that blockage of the β-1 and β-2 receptors in the ciliary body can reduce aqueous humor formation by as much as 50%. IOP reduction can usually be detected within 30 minutes after application. The peak action of timolol occurs in 1–2 hours and maintained for as long as 24 hours. The drug is partially metabolized in the liver and excreted by the kidneys.

The local side effects of timolol include but are not limited to conjunctival injection, discomfort, tearing, corneal hypoesthesia, and headache. The most common systemic side effects with the use of timolol are bradycardia, fatigue, dizziness, headache, and dyspnea. In addition to the more common side effects timolol use has been associated with arrhythmias, hypotension, masked hypoglycemia, decreased pulmonary function, bronchospasm, depression, somnolence and hypercholesterolemia.

The bioequivalence of the components of the combination product travoprost/timolol do not seem to be significantly different from that seen when the agents are administered separately. This is also true of the ocular and systemic plasma concentrations of the combined versus separate agents. The IOP changes appear similar with either morning or evening dosing.

Efficacy, Safety, and Tolerability
The safety and efficacy of the fixed combination medicine travoprost 0.004%/timolol 0.5% has been evaluated in numerous studies. The first study done in 2005 by Barnebey et al evaluated the safety and IOP-lowering efficacy of the FCM travoprost/timolol once a day to the separate components travoprost (PM dosing) and timolol (AM and PM dosing) in patients with open angle glaucoma or ocular hypertension. This results of this three-month treatment period revealed the FCM travoprost/timolol produced relevant IOP reductions that were greater than monotherapy with either travoprost or timolol alone. The FCM travoprost/timolol was shown to decrease the mean IOP from baseline 1.9–3.3 mmHg more than the timolol arm. Travoprost/timolol FCM was also shown to decrease the mean IOP 0.9–2.4 mmHg more than travoprost monotherapy alone. Just as importantly, the FCM travoprost/timolol had comparable adverse events and tolerability to travoprost or timolol alone.

A recent article again compared the IOP control of travoprost/timolol FCM to travoprost over a 24-hour period. The study was prospective, double-masked, crossover, active-controlled, randomized 24-hour comparison of thirty-two patients. Both medications were dosed in the evening in patients with primary open angle glaucoma over an eight-week period for each medication. The study revealed that the FCM travoprost/timolol had a lower absolute intraocular pressure level of 2.4 mmHg for the 24-hour curve at all time points compared with travoprost. In addition the FCM travoprost/timolol had a lower 24-hour mean IOP fluctuation and no statistical difference in adverse events compared to travoprost.

A study by Rossi et al compared concomitant latanoprost 0.005% and timolol 0.5% to the FCM travoprost/timolol by switching the two medications in patients with primary open angle glaucoma and
ocular hypertension. This six-month study was cohort involving 309 patients. The main outcomes were IOP measurements, tear breakup time, patients reaching IOP < 18 mmHg, the rate of discontinuation, and adverse events. The study revealed the IOP for patients on travoprost/timolol was 16.6 mmHg ±2.7 compared to an IOP of 18.3 mmHg ±2.9 on concomitant latanoprost and timolol. The tear breakup time showed improvement with travoprost/timolol with an average time of 9.2 s ±3.8 s compared to 8.4 s ±9.2 s with latanoprost and timolol. Eighty-two per cent of patients IOP was less than 18 mmHg. Adverse events (8.7% of patients) and discontinuation percentage (4.5%) were shown to be low in the study.

The FCM travoprost/timolol alone, was compared to evening dosed travoprost 0.004% monotherapy, and also compared to twice-daily brinzolamide 1% added to evening dosed travoprost/timolol by Hollo et al. The study involved 20 primary open angle or ocular hypertension patients. Patients received evening travoprost 0.004%, evening travoprost/timolol FCM, or evening dosed FCM travoprost/timolol with the addition of twice daily brinzolamide 1% (AM and PM dosing). The IOP was measured at baseline and at the end of each treatment period at four different times (8 AM, 12 NOON, 4 PM and 8 PM). The mean diurnal IOP at baseline was 28.5 mmHg with a standard deviation (SD) of 7.3 mmHg. The baseline IOP was decreased to 22.3 mmHg (6.3) with travoprost monotherapy, 19.2 mmHg (3.4) on the FCM travoprost/timolol, and 17.3 mmHg (3.4) when brinzolamide was added to the FCM of travoprost/timolol.

A study comparing two fixed combination medicines, travoprost/timolol and latanoprost/timolol, has been recently reported. The study was retrospective, cross-sectional, included a total of 316 patients (124 with travoprost/timolol, 192 with latanoprost/timolol), 266 of which used their drops in the last 24-hours prior to IOP measurement. The study found the travoprost/timolol groups mean IOP to be 17.2 mmHg versus 19.0 mmHg in the latanoprost/timolol group. Data on the patients that had taken their drops greater than 24-hours prior to IOP measurement also showed lower mean IOP’s in the travoprost/timolol group (17.0 mmHg) versus the latanoprost/timolol group (20.3 mmHg). The authors also reported that 82.6% of the travoprost/timolol patients had satisfied their target IOP’s versus 51.1% of the latanoprost/timolol patients.

A six-week observational study was done to compare four groups of patients being treated with topical IOP reduction therapy who were switched to the FCM travoprost/timolol. The four groups included those on timolol monotherapy, prostaglandin analog monotherapy, concomitant timolol and prostaglandin therapy, and patients on fixed combination medications. The study found that 87.9% of patients judged the tolerability of the FCM travoprost/timolol as good, very good, or excellent. Statistically significant reductions in IOP were found in each group.

The cost-efficacy of three fixed combination medications containing both timolol and a prostaglandin analog has been published. The study evaluated the combinations bimatoprost/timolol, latanoprost/timolol, and travoprost/timolol. This study calculated the average and incremental cost-efficacy ratios in terms of Euros per percentage point of reduction of IOP over a three-month period. It was found that the FCM bimatoprost/timolol reduced IOP by 35.1%, latanoprost/timolol FCM by 35.0%, and travoprost/timolol FCM by 34.7%. The average cost efficacy was estimated to be 5.34 Euro per percentage point of IOP reduction with bimatoprost/timolol, 5.40 Euro with latanoprost/timolol, and 5.45 Euro with travoprost/timolol. The authors report that the FCM bimatoprost/timolol appeared to be the most economic alternative with equal or better efficacy and safety profiles.

Schuman et al compared the efficacy and safety of the FCM travoprost/timolol to concomitant travoprost and timolol therapy, and to timolol monotherapy. The study was a prospective, randomized, multicenter, double-masked, parallel study of 403 patients randomized to receive either: FCM travoprost/timolol in the morning with placebo in the evening, timolol in the morning and travoprost in the evening, or timolol twice daily. The IOP was measured at 8 AM, 10 AM and 4 PM at weeks 2, 6, and 12 over a three-month period. The results were similar between the combination and concomitant therapy arms at the 8 AM measurement with an IOP reduction of—8.1–8.6 mmHg.
The concomitant treatment arm was slightly better than the combination treatment arm (7.3–8.4 mmHg versus 6.8–7.5 mmHg) at the 10 AM and 4 PM measurements. The combination and concomitant groups both revealed superior per-cent IOP reductions from baseline compared to timolol monotherapy. The IOP reductions from baseline were 29.1%–33.2% for the combination group, 31.5%–34.8% for the concomitant group, and 19.3%–27.0% for the timolol monotherapy group. Adverse events were similar between the combination and concomitant treatment groups.

Henry et al presented results of a comparison between the FCM travoprost/timolol and concomitant administration of latanoprost (Xalatan) and timolol 0.5%. The study was a randomized, single-center study that included patients currently taking concomitant PM latanoprost and AM timolol. These patients were either continued on their current concomitant regimen, or received AM FCM travoprost/timolol and PM placebo. The IOP was evaluated 3 months after treatment began at 4 time points, 8 AM, 10 AM, 4 PM, and 8 PM. The study found that 92% of the FCM travoprost/timolol and 88% of the patients in the concomitant latanoprost and AM timolol group maintained a clinically relevant IOP response (IOP < 18 mmHg). Adverse events were similar between the two groups. The results of the study revealed that patients who were previously controlled on concomitant timolol and latanoprost continue to have similar control if switched to the FCM travoprost/timolol.

The FCM travoprost/timolol was compared to concomitant travoprost 0.004% and timolol 0.5% in a randomized, multi-center, double-masked, active-controlled, parallel group study by Hughes et al. The study included 317 patients with open angle glaucoma or ocular hypertension. Participants were randomly assigned to the FCM travoprost/timolol in the AM or to timolol in the AM and travoprost in the PM for a 3 month period. The results revealed similar IOP reductions in both groups. The mean IOP for patients using the FCM travoprost/timolol ranged from 15.2–16.5 mmHg and 14.7–16.1 mmHg in the concomitant travoprost and timolol group. The mean IOP reductions from baseline for the travoprost/timolol group ranged from 7.4–9.4 mmHg and 8.4 to 9.4 mmHg with the concomitant travoprost and timolol therapy. Again, the safety and tolerability of the two groups was similar.

Two fixed combinations, both containing a prostaglandin analog + timolol were compared by Topouzia et al. The study compared the FCM travoprost 0.004%/timolol 0.5% to the FCM latanoprost 0.005%/timolol 0.5%. The study was a randomized, double-masked, multicenter, parallel group, active-controlled study with a total of 408 patients. One of the two medications was administered each morning at 9 AM and IOP was measured at 9 AM at week 2, week 6, month 3, and month 9. The IOP was measured at 9 AM, 11 AM, and 4 PM during months 6 and 12 of the study. The mean IOP was found to be lower for the travoprost/timolol group (16.4–17.1 mmHg; 38% reduction from baseline) compared to the latanoprost/timolol group (16.7–17.1 mmHg; 37% reduction from baseline) at all of the 10 study visits. There was no statistically significant difference in adverse events between the groups.

Two studies that evaluated the optimal timing for administration of the FCM travoprost 0.004%/timolol 0.5% have been reported by Denis et al and Konstas et al. The studies suggested that PM dosing of the FCM travoprost/timolol contributes to lower mean IOP and a lower 24-hour IOP curve. The study by Denis et al was a 6-week, prospective, randomized, double masked, parallel group study of 92 patients either assigned AM or PM dosing of the FCM travoprost/timolol. The results revealed both groups to have mean IOP reductions of 32%–38% with the mean IOP for the morning arm ranging from 16.5–16.7 mmHg and the mean IOP for the evening arm to be 16.1–17.2 mmHg. The study by Konstas et al plotted the 24-hour IOP curve of 32 patients taking AM or PM travoprost/timolol FCM at the end of 8 weeks of treatment. The intraocular pressures of each patient were taken at 2 AM, 6 AM, 10 AM, 2 PM, 6 PM and 10 PM to plot the 24-hour curve. The patients dosing was then switched (AM to PM, or PM to AM) to the opposite time for an additional 8 weeks and the 24-hour curve repeated. The study found the evening dose had a statistically significant lower 24-hour IOP curve of 18.4 mmHg versus 19.2 mmHg for the morning-dosed arm. The evening dosing also had lower 24-hour fluctuations (20.4 mmHg versus 21.7 mmHg).

**Patient Focused Perspectives**
Clinical trials guide physicians’ decision making by presenting comparative information on a specific
treatment or therapy. However, the environment and nature with which they are conducted can overlook problems that are often encountered in clinical practice. For example, poorly adherent patients are dropped from the studies, patients who do not meet eligibility requirements are excluded, clinical services, parking fees, and medications are provided free of charge, and many patients are controlled with monotherapy. The reality is that many patients are not adherent to therapy. The OHTS study found that after 5 years of treatment nearly 40% of glaucoma patients need to use 2 or more medications to control their IOP. The FCM travoprost/timolol offers the IOP lowering combination of two separate classes of medications into one bottle, with once a day dosing. This simplified dosing regimen helps reduce the potential barrier of forgetfulness and confusion as a reason for noncompliance.

The inferior fornix can only accommodate ~30 microliters of fluid. Drug washout is an important factor to consider when dosing multiple medications with liquid volumes of 40–50 micro-liters into a space the size of the inferior fornix. The possibility of a drop volume washout of greater than or equal to 50% of the first medication could occur if the second medication is not properly administered. Once again, the FCM travoprost/timolol may prevent this potential problem with one drop dosing.

The factor of medication costs is well-recognized barrier to glaucoma treatment compliance. The costs of a FCM would be expected to be lower than purchasing each medication separately. In addition, managed-care patients would only be subject to a single co-payment with the FCM travoprost/timolol rather than two separate co-payments for the separate products.

A fixed combination topical glaucoma medication reduces further exposure of the ocular surface to the effects of preservatives present in glaucoma medications, often BAK. Monotherapy thus limits cumulative exposure to preservatives and could subsequently reduce the incidence and severity of ocular surface-related side effects, and potentially lead to improved medication compliance.

Conclusion, Place in Therapy
The FCM travoprost/timolol is a potent beta-blocker and prostaglandin analog eye drop that has been proven in numerous studies to be effective in IOP lowering and a well tolerated profile. Use of this FCM as a first-line agent should be used with caution because of the potential to expose the patient to unnecessary potential side effects of the second medication. A FCM like travoprost/timolol offers several potential advantages. These include simpler dosing regimens, reduced cost, and decreased preservative-related side effects.

Disclosures
This manuscript has been read and approved by all authors. This paper is unique and is not under consideration by any other publication and has not been published elsewhere. Dr Noecker is a consultant to Alcon. The peer reviewers of this paper report no conflicts of interest. The authors confirm that they have permission to reproduce any copyrighted material.

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