

PRODUCT MONOGRAPH

***DuoTrav<sup>TM</sup>***

**(travoprost and timolol maleate)  
Ophthalmic Solution  
travoprost 0.004%, timolol 0.5%**

THERAPEUTIC CLASSIFICATION:

Elevated Intraocular Pressure Therapy

**Prostaglandin F<sub>2α</sub> analogue and beta-adrenergic receptor blocker**

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### **ACTION & CLINICAL PHARMACOLOGY**

#### **Mechanism of Action**

*DuoTrav* (travoprost/timolol) Ophthalmic Solution contains two active components, travoprost and timolol maleate, which lower intraocular pressure by complementary mechanisms of action.

Travoprost free acid is a highly selective FP prostanoid receptor agonist that has been shown to reduce intraocular pressure by increasing uveoscleral and conventional outflow. Reduction of intraocular pressure starts within approximately two hours after administration, and the maximum effect is reached after 12 hours. Significant lowering of intraocular pressure can be maintained for periods exceeding 24 hours with a single dose. Repeated observations over a period of one year indicate that the intraocular pressure lowering effect of travoprost is well maintained.

Timolol maleate is a beta<sub>1</sub> and beta<sub>2</sub> (non-selective) adrenergic receptor blocking agent that does not have significant intrinsic sympathomimetic, direct myocardial depressant, or local anesthetic (membrane-stabilizing) activity. The precise mechanism of the ocular hypotensive action of timolol is not definitively established. Tonography and fluorophotometry studies in man suggest that its predominant action is related to reduced aqueous humor formation. However, in some studies a slight increase in outflow facility was also observed. The onset of reduction of intraocular pressure following administration of timolol can usually be detected within one-half hour after a single dose. The maximum effect usually occurs in one to two hours and significant

lowering of intraocular pressure can be maintained for periods as long as 24 hours after a single dose. Repeated observations over a period of one year indicate that the intraocular pressure-lowering effect of timolol is well maintained.

### **Pharmacokinetics/Pharmacodynamics**

*DuoTrav* (travoprost/timolol) Ophthalmic Solution, when applied topically to the eye, has the action of reducing elevated as well as normal intraocular pressure, whether or not accompanied by glaucoma. Elevated intraocular pressure is a major risk factor in the pathogenesis of glaucomatous visual field loss. The higher the level of intraocular pressure, the greater the likelihood of glaucomatous visual field loss and optic nerve damage. The Advanced Glaucoma Intervention Study (AGIS) (1) established elevated intraocular pressure as a positive risk factor for glaucomatous visual field loss. Eyes with intraocular pressures below 18 mmHg at all visits were found to have little to no visual field loss during the six-year monitoring period.

**Absorption:** Travoprost and timolol are absorbed through the cornea. Travoprost undergoes rapid ester hydrolysis in the cornea to the active free acid. In travoprost studies, peak plasma concentrations of the free acid were observed within 30 minutes after dosing. Following topical ocular administration of *DuoTrav* solution once-daily in healthy subjects (N = 15) for 3 days, the travoprost free acid was not quantifiable in plasma samples from the majority of subjects (80%, N=12/15) and was not detectable in any samples one hour after dosing. In those subjects in whom travoprost free acid was measurable ( $\geq 0.01$  ng/mL, the assay limit of quantitation), plasma concentration ranged from 0.010 to 0.020 ng/mL. The mean peak timolol steady-state concentration was  $0.692 \text{ ng/mL} \pm 0.384 \text{ ng/mL}$  after once-daily administration of *DuoTrav*. Timolol  $T_{\text{max}}$  was observed within one hour after dosing.

**Distribution:** Travoprost free acid can be measured in the aqueous humor during the first few hours in animals and in human plasma only during the first hour after topical ocular administration of *DuoTrav*. Timolol can be measured in human aqueous humor after topical ocular administration of timolol and in plasma for up to 12 hours after topical ocular administration of *DuoTrav*.

**Metabolism:** Travoprost, an isopropyl ester prodrug, is hydrolyzed by esterases in the cornea to its pharmacologically active free acid. Systemically, travoprost free acid is metabolized to inactive metabolites via beta-oxidation of the  $\alpha$ (carboxylic acid) chain to give the 1,2-dinor and 1,2,3,4-tetranor analogs, via oxidation of the 15-hydroxyl moiety, as well as via reduction of the 13,14 double bond in primates. The plasma elimination of the free acid was rapid with a mean apparent  $t_{1/2}$  of approximately 45 minutes. There was no difference in plasma concentrations between Days 1 and 3, indicating steady-state was reached early and there was no accumulation.

In humans, timolol is primarily metabolized by two pathways involving ring-opening oxidation of the morpholine ring. One route yields an ethanolamine side chain on the thiadiazole ring and the other giving an ethanolic side chain on the morpholine nitrogen and a second similar side chain with a carbonyl group adjacent to the nitrogen (2,3). The apparent terminal elimination  $t_{1/2}$  of timolol in plasma is approximately 4 hours after topical ocular administration of *DuoTrav*.

**Excretion:** Travoprost free acid and its metabolites are mainly excreted by the kidneys. In humans, less than 2% of a topical ocular dose of travoprost was recovered in urine as free acid. Timolol and its metabolites are primarily excreted by the kidneys. Approximately 20% of a timolol dose is excreted in the urine unchanged and the remainder excreted in urine as metabolites (2).

For efficacy and safety information for *DuoTrav* obtained from clinical trials, please refer to the subsection Clinical Trials in the **PHARMACOLOGY** section.

## INDICATIONS AND CLINICAL USE

*DuoTrav* (travoprost/timolol) Ophthalmic Solution is indicated for the reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension who are insufficiently responsive to beta-blockers, prostaglandins, or other IOP lowering agents AND when the use of *DuoTrav* (the fixed combination drug) is considered appropriate.

*DuoTrav* should not be used to initiate therapy.

The use of DuoTrav is not recommended for paediatric patients.

For details of information obtained from Clinical Trials with *DuoTrav*, please refer to Clinical Trials subsection under **PHARMACOLOGY**. Also see **DOSAGE AND ADMINISTRATION**.

## CONTRAINDICATIONS

NOTE: *DuoTrav* is a combination of travoprost 0.004% and timolol 0.5% as timolol maleate. When *DuoTrav* is prescribed, the relevant Product Monographs for travoprost and/or timolol maleate should be consulted.

*DuoTrav* (travoprost/timolol) Ophthalmic Solution is contraindicated in patients who:

- are hypersensitive to this drug or to any ingredient in the formulation (see **Composition**) or component of the container.
- have bronchial asthma
- have a history of bronchial asthma
- have severe chronic obstructive pulmonary disease (see **WARNINGS**)
- have sinus bradycardia
- have second or third degree atrioventricular block

- have overt cardiac failure (see **WARNINGS**)
- have cardiogenic shock

## **WARNINGS**

### **FOR TOPICAL OPHTHALMIC USE ONLY.**

NOTE: *DuoTrav* is a combination of travoprost 0.004% and timolol 0.5% as timolol maleate. When *DuoTrav* is prescribed, the relevant Product Monographs for travoprost and/or timolol maleate should be consulted.

If signs of serious reactions or hypersensitivity occur, discontinue use of this preparation.

### **Ocular Effects**

Travoprost and other prostaglandin analogues have been reported to cause changes to pigmented tissues. The most frequently reported changes have been increased pigmentation of the iris and periorbital tissue (eyelid) and increased pigmentation and growth of eyelashes. These changes may be permanent.

*DuoTrav* (travoprost/timolol) Ophthalmic Solution may gradually change eye colour, increasing the amount of brown pigmentation in the iris. The colour change is due to increased melanin content in stromal melanocytes on the iris rather than to an increase in the number of melanocytes, although the exact mechanism of action is unknown at this time. Typically the brown pigmentation around the pupil spreads concentrically towards the periphery in affected eyes, but the entire iris or parts of it may become more brown. Iris pigmentation changes may be more noticeable in patients with mixed coloured irides, i.e., blue-brown, grey-brown, yellow-brown, and green-brown, however, it has also been observed in patients with brown eyes. The change in iris colour occurs slowly and may not be noticeable for several months to years. The long-term effects on the melanocytes and the consequences of potential injury to the melanocytes and/or deposition of pigment granules to other areas of the eye are currently unknown. Patients

should be informed of the possibility of iris colour change since the increased pigmentation is permanent. Patients should be examined regularly and, depending on the clinical situation, treatment may be stopped if increased pigmentation ensues.

Eyelid skin darkening has been reported in association with the use of *DuoTrav*. *DuoTrav* solution may gradually change eyelashes in the treated eye; these changes include increased length, thickness, pigmentation, and/or number of lashes.

Patients who are expected to receive treatment in only one eye should be informed about the potential for increased brown pigmentation of the iris, periorbital and/or eyelid tissue, and eyelashes in the treated eye and thus heterochromia between the eyes. They should also be advised of the potential for a disparity between the eyes in length, thickness, and/or number of eyelashes.

### **Systemic Effects**

The same adverse reactions found with systemic administration of beta-adrenergic blocking agents may occur with topical administration of *DuoTrav* due to the beta-adrenergic component, timolol. For example, severe respiratory reactions and cardiac reactions, including death due to bronchospasm in patients with asthma, and rarely death in association with cardiac failure, have been reported following systemic or ophthalmic administration of timolol maleate (see **CONTRAINDICATIONS**).

### **Cardiac Failure**

Because of the timolol maleate component, cardiac failure should be adequately controlled before beginning treatment with *DuoTrav*. Patients with a history of severe cardiac disease should be watched for signs of cardiac failure and have their pulse rates checked.

Caution should be exercised in treating patients with severe cardiovascular disease.

### **Anaphylaxis**

While taking beta-blockers, patients with a history of atopy or a history of severe anaphylactic reactions to a variety of allergens may be more reactive to repeated accidental, diagnostic, or therapeutic challenge with such allergens. Such patients may be unresponsive to the usual doses of epinephrine used to treat anaphylactic reactions.

### **Obstructive Pulmonary Disease**

Patients with chronic obstructive pulmonary disease (e.g., chronic bronchitis, emphysema) of mild or moderate severity, bronchospastic disease, or a history of bronchospastic disease (other than bronchial asthma or a history of bronchial asthma, in which *DuoTrav* is contraindicated [see **CONTRAINDICATIONS**]) should, in general, not receive beta-blockers or products containing them, including *DuoTrav*.

### **Diabetes Mellitus**

Beta-adrenergic blocking agents should be administered with caution in patients subject to spontaneous hypoglycemia or to diabetic patients (especially those with labile diabetes) who are receiving insulin or oral hypoglycemic agents. Beta-adrenergic receptor blocking agents may mask the signs and symptoms of acute hypoglycemia.

### **Angle-closure Glaucoma**

*DuoTrav* should not be used alone in the treatment of acute angle-closure glaucoma.

### **Concomitant Therapy**

Timolol may interact with other drugs (see also information under **Drug Interactions**). The effect on intraocular pressure or the known effects of systemic beta-blockers may be exaggerated when *DuoTrav* is given to patients already receiving an oral beta-blocking agent. The use of two local beta-blockers or two local prostaglandins is not recommended.

### **Use in Pregnancy**

No adequate and well-controlled studies have been performed in pregnant women. *DuoTrav* ophthalmic solution should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

### **Teratogenic Effects**

Travoprost was teratogenic in rats. Travoprost administered intravenously to pregnant rats from gestation Days 6-17 at a dose of 10 µg/kg/day, induced a slight increase in the incidence of skeletal malformations such as fused sternebrae, domed head and hydrocephaly. No effect was observed at 3 µg/kg/day (75 times the maximum recommended human dose (MRHOD) of 0.04 µg/kg/day). The no effect level for fetal external, visceral or skeletal malformation was observed after 1.0 µg/kg/day subcutaneous administration during gestation days 6-16 to pregnant mice, though postimplantation loss was increased at that dose, but not at 0.3 µg/kg/day.

Teratogenicity studies with timolol in mice, rats, and rabbits at oral doses up to 50 mg/kg/day (7,000 times the MRHOD demonstrated no evidence of fetal malformations. Although delayed fetal ossification was observed at this dose in rats, there were no adverse effects on postnatal development of offspring. Doses of 1000 mg/kg/day (142,000 times the MRHOD) were maternotoxic in mice and resulted in an increased number of fetal resorptions. Increased fetal resorptions were also seen in rabbits at doses of 14,000 times the MRHOD, in this case without apparent maternotoxicity.

For additional information see **TOXICOLOGY** section.

### **Use in Paediatrics**

The use of *DuoTrav* in paediatric patients is currently not recommended. The safety and efficacy of the use of *DuoTrav* in children has not been established.

## PRECAUTIONS

NOTE: *DuoTrav* is a combination of travoprost 0.004% and timolol 0.5% as timolol maleate. When *DuoTrav* is prescribed, the relevant Product Monographs for travoprost and/or timolol maleate should be consulted.

### General

Patients prescribed IOP-lowering medication should be routinely monitored for IOP status.

Patients may slowly develop increased brown pigmentation of the iris. This change is permanent and may not be noticeable for months to years (see **WARNINGS**).

*DuoTrav* should be used with caution in patients with active intraocular inflammation (iritis/uveitis).

Macular edema, including cystoid macular edema, has been reported during treatment with prostaglandin F<sub>2α</sub> analogues such as travoprost. These reports have mainly occurred in aphakic patients, pseudophakic patients with a torn posterior lens capsule, or in patients with known risk factors for macular edema. *DuoTrav* Ophthalmic Solution should be used with caution in these patients.

### Contact Lenses

*DuoTrav* contains the preservative benzalkonium chloride, which may be deposited in soft contact lenses; therefore, *DuoTrav* should not be administered while wearing these lenses. The lenses should be removed before application of the drops and not be reinserted earlier than 15 minutes after use.

### Choroidal Detachment

Choroidal detachment after filtration procedures has been reported with administration of aqueous suppressant therapy (e.g., timolol maleate, acetazolamide). Management of eyes with

chronic or recurrent choroidal detachment should include stopping all forms of aqueous suppressant therapy and treating endogenous inflammation vigorously.

### **Major Surgery**

The necessity or desirability of withdrawal of beta-adrenergic blocking agents prior to major surgery is controversial. If necessary during surgery, the effects of beta-adrenergic blocking agents may be reversed by sufficient doses of such agonists as isoproterenol, dopamine, dobutamine or levarterenol.

### **Thyrotoxicosis**

Beta-adrenergic blocking agents may mask certain clinical signs of hyperthyroidism (e.g., tachycardia). Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta-adrenergic blocking agents that might precipitate a thyroid storm.

### **Muscle Weakness**

Beta-adrenergic blockade has been reported to increase muscle weakness consistent with certain myasthenic symptoms (e.g., diplopia, ptosis and generalized weakness). Timolol maleate has been reported rarely to increase muscle weakness in some patients with myasthenia gravis or myasthenic symptoms.

### **Cerebrovascular Insufficiency**

Because of potential effects of beta-adrenergic blocking agents on blood pressure and pulse, these agents should be used with caution in patients with cerebrovascular insufficiency. If signs or symptoms suggesting reduced cerebral blood flow develop following initiation of therapy with *DuoTrav*, alternative therapy should be considered.

### **Renal/Hepatic Impairment**

*DuoTrav* has not been studied in patients with renal impairment; caution should be exercised in treating such patients.

### **Use in Pregnancy**

There are no adequate and well-controlled studies of *DuoTrav* in pregnant women. Because animal reproduction studies are not always predictive of human response, *DuoTrav* should be used during pregnancy only if the potential benefit to the mother justifies potential risk to the fetus. See **WARNING** section.

### **Nursing Mothers**

Timolol maleate has been detected in human milk following oral and ophthalmic drug administration. It is not known whether travoprost and/or its metabolites are excreted in human milk, although in animal studies, travoprost has been shown to be excreted in milk. Because of the potential for serious adverse reactions from timolol maleate or travoprost in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

### **Use in Paediatrics**

The use of *DuoTrav* in paediatric patients is currently not recommended. The safety and efficacy of the use of *DuoTrav* in children has not been established (see **WARNINGS**).

### **Use in the Elderly**

No overall differences in safety or effectiveness have been observed between elderly and other adult patients.

### **Driving or Using Machinery**

*DuoTrav*, as with other similar medications, can potentially cause fatigue and/or drowsiness in some patients. Patients who engage in hazardous activities should be cautioned of the potential for a decrease in mental alertness.

### **Drug Interactions**

No specific interaction studies have been performed with *DuoTrav*.

Beta-adrenergic blocking agents: Patients who are receiving a beta-adrenergic blocking agent orally and *DuoTrav* should be observed for potential additive effects of beta-blockade, both systemic and on intraocular pressure. The concomitant use of two topical beta-adrenergic blocking agents is not recommended.

Calcium antagonists: Caution should be used in the coadministration of beta-adrenergic blocking agents, such as the timolol found in *DuoTrav*, and oral or intravenous calcium antagonists because of possible atrioventricular conduction disturbances, left ventricular failure, and hypotension. In patients with impaired cardiac function, coadministration should be avoided.

Catecholamine-depleting drugs: Close observation of the patient is recommended when a beta blocker is administered to patients receiving catecholamine-depleting drugs such as reserpine, because of possible additive effects and the production of hypotension and/or marked bradycardia, which may result in vertigo, syncope, or postural hypotension.

Digitalis and calcium antagonists: The concomitant use of beta-adrenergic blocking agents with digitalis and calcium antagonists may have additive effects in prolonging atrioventricular conduction time.

Quinidine: Potentiated systemic beta-blockade (e.g., decreased heart rate) has been reported during combined treatment with quinidine and timolol, possibly because quinidine inhibits the metabolism of timolol via the P-450 enzyme, CYP2D6.

Clonidine: Oral beta-adrenergic blocking agents may exacerbate the rebound hypertension which can follow the withdrawal of clonidine. There have been no reports of exacerbation of rebound hypertension with ophthalmic timolol maleate (4).

Injectable epinephrine: (See **WARNINGS, Anaphylaxis**)

CNS Depressants: Although specific drug interaction studies have not been conducted with *DuoTrav*, the possibility of an additive or potentiating effect with CNS depressants (alcohol, barbiturates, opiates, sedatives, or anesthetics) should be considered.

Tricyclic Antidepressants: Tricyclic antidepressants have been reported to blunt the hypotensive effect of systemic clonidine. It is not known whether the concurrent use of these agents with *DuoTrav* can lead to an interference in IOP lowering effect.

No data are available on the level of circulating catecholamines after *DuoTrav* is instilled. Caution, however, is advised in patients taking tricyclic antidepressants which can affect the metabolism and uptake of circulating amines.

Epinephrine: Mydriasis resulting from concomitant use of timolol maleate and epinephrine has been reported occasionally.

### **Information to be Provided to the Patient by the Physician**

Patients should be advised to carefully take note of the proper use of the medication and other precautions contained in the package insert.

Patients with bronchial asthma, a history of bronchial asthma, severe chronic obstructive pulmonary disease, sinus bradycardia, second- or third-degree atrioventricular block, cardiac failure, or patients receiving monoamine oxidase (MAO) inhibitor therapy should be advised not to take this product (see **CONTRAINDICATIONS**).

Patients should be instructed to avoid allowing the tip of the dispensing container to contact the eye or surrounding structures. If handled improperly, ocular solutions can become contaminated by common bacteria known to cause ocular infections. Serious damage to the eye and subsequent loss of vision may result from using contaminated solutions.

There have been reports of bacterial keratitis associated with the use of multiple dose containers of topical ophthalmic products. These containers had been inadvertently contaminated by patients who, in most cases, had a concurrent corneal disease or a disruption of the ocular epithelial surface.

Patients should also be advised that if they have ocular surgery or develop an intercurrent ocular condition (e.g., trauma or infection), they should immediately seek their physician's advice concerning the continued use of the present multidose container.

If more than one topical ophthalmic drug is being utilized, the drugs should be administered at least ten minutes apart.

Patient wearing Contact Lenses

The preservative in *DuoTrav*, benzalkonium chloride, may be absorbed by soft (hydrophilic) contact lenses. Patients wearing soft contact lenses should be instructed to wait at least 15 minutes after instilling *DuoTrav* to insert soft contact lenses.

## **ADVERSE REACTIONS**

### **Clinical Trial Adverse Drug Reactions**

#### **Adverse Drug Reaction Overview**

In clinical trials 721 subjects/patients were exposed to *DuoTrav* (travoprost/timolol) Ophthalmic Solution administered once-daily for up to 12 months. This included 15 subjects with short-term exposure in a single pharmacokinetic study and 706 patients with open-angle glaucoma or ocular hypertension in long-term studies. No serious ophthalmic or systemic adverse reactions specifically related to *DuoTrav* were reported in any study. The adverse drug reactions are limited to those reported previously with travoprost and/or timolol maleate. In the clinical trials 4.6% of patients discontinued therapy with *DuoTrav* due to adverse drug reactions.

## **Clinical Trial Adverse Drug Reactions**

*Because clinical trials are conducted under very specific conditions the adverse drug reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.*

### **Adverse Drug Reactions in Clinical Trials Providing Short-Term Exposure**

In a single pharmacokinetic trial of crossover design (C-02-35), 15 subjects had short-term exposure (3 days) to *DuoTrav*. The most frequently reported adverse drug reaction was ocular hyperaemia. No subject discontinued therapy as a result of any adverse drug reaction in this study and no subject experienced a serious adverse drug reaction.

**Table 1: All Adverse Drug Reactions Occurring in Subjects with Exposure to *DuoTrav* - Short-Term Study (C-02-35)**

	<i>DuoTrav</i> N=15 %	TRAVATAN N=15 %	Timolol 0.5% N=14 %
<b><i>Eye disorders</i></b>			
Ocular hyperaemia	86.7	46.7	28.6
Eye irritation	13.3	13.3	
Eye pruritus	6.7		
Eyelids pruritus	6.7		
Abnormal sensation in eye	6.7	6.7	
Blurred vision	6.7		7.1
<b><i>Respiratory, thoracic and mediastinal disorder</i></b>			
Postnasal drip	6.7	6.7	7.1
<b><i>General disorders and administration site conditions</i></b>			
Thirst	6.7		
<b><i>Investigations</i></b>			
Intraocular pressure decreased	6.7		

Adverse drug reactions coded using MedDRA version 8.0  
This table includes all reported ocular and non-ocular adverse drug reactions.

Less Common Clinical Trial Adverse Drug Reactions (<1%) in Subjects with Short-Term Exposure to *DuoTrav*

Due to the small sample size in this trial, a single reported adverse drug reaction in the *DuoTrav* or TRAVATAN treatment group resulted in an incidence of 6.7%, while in the Timolol treatment group a single adverse drug reaction resulted in an incidence of 7.1%.

Adverse Drug Reactions in Clinical Trials Providing Long-Term Exposure

In 5 clinical trials (C-01-69, C-01-70, C-02-03, C-02-28, and C-02-41), 706 patients with open-angle glaucoma or ocular hypertension had long-term exposure (6 weeks to 1 year) to *DuoTrav*. No serious ophthalmic or systemic adverse drug reactions related to *DuoTrav* were reported in any trial providing long-term exposure. The most frequently reported adverse drug reaction was ocular hyperaemia (13.9%). Almost all patients (98%) who experienced ocular hyperaemia did not discontinue therapy as a result of this reaction. Additional adverse drug reactions that occurred at an incidence of  $\geq 1.0\%$  in patients with long-term exposure to *DuoTrav* included the following:

**Table 2: Adverse Drug Reactions Occurring at an Incidence of  $\geq 1\%$  in Patients with Exposure to *DuoTrav* - Long-Term Studies (C-01-69, C-01-70, C-02-03, C-02-28, C-02-41)**

	<i>DuoTrav</i> N=706 %	Latanoprost 0.005%/ Timolol 0.5% N=200 %	TRAVATAN + Timolol 0.5% N=313 %	TRAVATAN N=86 %	Timolol 0.5% N=176 %
<b><i>Eye Disorders</i></b>					
Ocular hyperaemia	13.9	2.5	18.8	11.6	1.7
Eye irritation	6.1	3.0	10.9	5.8	5.7
Eye pruritis	4.5	2.0	4.8	2.3	0.5
Dry eye	2.5	1.0	2.9	2.3	1.7
Abnormal sensation in eye	2.3	3.5	2.9	2.3	1.7
Growth of eyelashes	1.6	-	2.2	1.2	-
Eye pain	1.3	0.5	-	-	-
Photophobia	1.3	-	1.6	1.2	-
Blurred vision	1.1	-	1.6	-	2.8
Punctate keratitis	1.0	0.5	1.9	1.2	-

Adverse drug reactions coded using MedDRA version 8.0

No non-ocular adverse drug reactions occurred at an incidence  $\geq 1\%$ .

In a twelve month study with *DuoTrav* ocular photographs were taken of the iris using a standardized procedure and evaluated by a centralized reading center masked to study treatment in order to assess effects on iris pigmentation. Following an initial latent period the incidence of iris pigmentation changes increased in both treatment groups from Month 6 to Month 12 as shown in the following table.

**Table 3: Patients with Iris Pigmentation Changes<sup>a</sup> (C-02-28)**

	<i>DuoTrav</i>		Latanoprost 0.005%/ Timolol 0.5%		
	N <sup>c</sup>	%		N <sup>c</sup>	%
Month 6 (N=169) <sup>b</sup>	1	0.6	Month 6 (N=161) <sup>b</sup>	1	0.6
Month 12 (N=166) <sup>b</sup>	4	2.4	Month 12 (N=163) <sup>b</sup>	2	1.2

<sup>a</sup> Changes based upon review of ocular photographs by a centralized reading center

<sup>b</sup> N values represent number of patients with ocular photographs

<sup>c</sup> N values represent number of patients with iris pigmentation changes

(See also **PHARMACOLOGY; CLINICAL TRIALS**)

Less Common Clinical Trial Adverse Drug Reactions (<1%) in Patients with Long-Term Exposure to *DuoTrav*

Adverse drug reactions that occurred at an incidence of <1.0% in patients with long-term exposure to *DuoTrav* included the following:

**Table 4: Adverse Drug Reactions Occurring at an Incidence of < 1% in Patients with Exposure to *DuoTrav* - Long-Term Studies (C-01-69, C-01-70, C-02-03, C-02-28, C-02-41)**

MedDRA SOC	MedDRA PT
<i>Psychiatric disorders</i>	nervousness
<i>Nervous system disorders</i>	dizziness, headache
<i>Eye disorders</i>	anterior chamber cells, anterior chamber flare, dermatitis eyelid, erythema of eyelid, ocular discomfort, periorbital disorder, asthenopia, eyelids pruritus, visual acuity reduced, conjunctival haemorrhage, conjunctivitis allergic, eye swelling, eyelid irritation, eyelid oedema, eyelid pain, lacrimation increased, visual disturbance, corneal staining, blepharitis, conjunctival oedema, eye allergy, xerophthalmia
<i>Vascular disorders</i>	hypertension
<i>Respiratory, thoracic and mediastinal disorders</i>	postnasal drip, bronchospasm, cough, dyspnoea, throat irritation
<i>Skin and subcutaneous tissue disorders</i>	skin hyperpigmentation, dermatitis contact, distichiasis, hypertrichosis, urticaria
<i>Musculoskeletal and connective tissue disorders</i>	pain in extremity
<i>Renal and urinary disorders</i>	chromaturia
<i>General disorders and administration site conditions</i>	thirst
<i>Investigations</i>	alanine aminotransferase increased <sup>a</sup> , aspartate aminotransferase increased <sup>a</sup> , blood pressure diastolic decreased, blood pressure diastolic increased, blood pressure increased, heart rate decreased, heart rate irregular, intraocular pressure decreased

<sup>a</sup> No clinical laboratory evaluations were performed. These adverse drug reactions were based upon patient reports. Adverse drug reactions are presented in order of decreasing incidence; when reactions occurred at the same incidence they are presented alphabetically.

Adverse drug reactions coded using MedDRA version 8.0

SOC = System Organ Class

PT = Preferred term

## **Additional Adverse Drug Reactions Observed with the Individual Components of DuoTrav**

The following additional adverse drug reactions have been seen with one of the individual components of *DuoTrav* (TRAVATAN or Timolol), have not been presented in the preceding tables or text, and may potentially occur with *DuoTrav*. For further detailed information, please consult the individual Product Monographs for TRAVATAN or Timolol.

**Table 5: Additional Adverse Drug Reactions Previously Observed in One of the Individual Components and That May Potentially Occur with *DuoTrav***

	<b>TRAVATAN</b>	<b>Timolol</b>
<b>MedDRA SOC</b>	<b>MedDRA PT</b>	<b>MedDRA PT</b>
<i>Metabolism and nutrition disorders</i>	-	hypoglycemia
<i>Psychiatric disorders</i>	-	depression
<i>Nervous system disorders</i>	-	cerebrovascular accident, cerebral ischaemia, myasthenia gravis, syncope, paresthesia
<i>Eye disorders</i>	asthenopia, conjunctivitis, conjunctival follicles, conjunctival disorder, eyelid margin crusting, eyelid oedema, iris hyperpigmentation, iritis, macular oedema, uveitis	conjunctivitis, corneal disorder, diplopia, eyelid ptosis
<i>Cardiac disorders</i>	-	arrhythmia, atrioventricular block, cardiac arrest, cardiac failure, palpitations
<i>Vascular disorders</i>	hypotension	hypotension
<i>Respiratory, thoracic and mediastinal disorders</i>	asthma	nasal congestion, respiratory failure
<i>Gastrointestinal disorders</i>	-	diarrhoea, nausea
<i>Skin and subcutaneous tissue disorders</i>	hair growth abnormal, skin discolouration	alopecia, rash
<i>General disorders and administration site conditions</i>	-	asthenia, chest pain

Adverse drug reactions coded using MedDRA version 8.0

SOC = System Organ Class

PT = Preferred term

## **Abnormal Hematologic and Clinical Chemistry Findings**

No clinical laboratory evaluations for the analysis of safety were performed during the clinical development of *DuoTrav*. The clinical laboratory adverse drug reactions presented in Table 4

were based upon patient reports. For further information, please consult the individual Product Monographs for TRAVATAN or Timolol.

**Post-Market Adverse Drug Reactions**

The individual components TRAVATAN® (travoprost ophthalmic solution, 0.004%) and Timolol (timolol maleate ophthalmic solution, 0.1%, 0.25%, and 0.5%) are registered in numerous countries. Based upon a review of spontaneous post-marketing reports of adverse events to date, TRAVATAN and Timolol are well-tolerated and safe for use as indicated.

In post-market, a few reports of iritis/uveitis associated with the use of travoprost have been published. These cases occurred a few days after travoprost use in patients without a history of iritis/uveitis. All of these cases resolved after stopping travoprost with or without corticosteroid treatment.

As spontaneous event reports frequently provide incomplete data, report of a spontaneous event does not necessarily constitute an admission that TRAVATAN or Timolol caused or contributed to the event.

The following additional adverse drug reactions (presented in alphabetical order), not presented in the preceding tables or text, have been reported via postmarketing surveillance with one of the individual components of *DuoTrav* (TRAVATAN or Timolol) and may potentially occur with *DuoTrav*.

**Table 6: Additional Adverse Drug Reactions Reported Via Postmarketing Surveillance for One of the Individual Components and That May Potentially Occur with *DuoTrav***

	<b>TRAVATAN</b>	<b>Timolol</b>
<b><i>MedDRA SOC</i></b>	<b>MedDRA PT</b>	<b>MedDRA PT</b>
<i>Infections and infestations</i>	herpes simplex ophthalmic, influenza, urinary tract infection NOS	conjunctivitis infective, eye infection
<i>Neoplasms benign, malignant and unspecified</i>	gastrointestinal carcinoma	

<i>(incl cysts and polyps)</i>		
<i>Blood and lymphatic system disorders</i>	thrombocytopenia	
<i>Immune system disorders</i>	anaphylactic shock, hypersensitivity NOS	hypersensitivity
<i>Endocrine disorders</i>	hirsutism	
<i>Metabolism and nutrition disorders</i>	hyperglycaemia NOS, hypoglycaemia NOS, weight fluctuation	
<i>Psychiatric disorders</i>	aggression, anxiety, anxiety aggravated, depression aggravated, insomnia, sleep disorder NOS	
<i>Nervous system disorders</i>	amnesia, aphonia, cerebrovascular accident, dysgeusia, epilepsy NOS, facial neuralgia NOS, hypertonia, hypoaesthesia, hypokinesia, loss of consciousness, memory impairment, migraine NOS, motor dysfunction NOS, paraesthesia, paresis, somnolence, syncope, tremor, vasovagal attack	dysgeusia, somnolence
<i>Eye disorders</i>	accommodation disorder, angle closure glaucoma, anterior chamber disorder NOS, anterior chamber pigmentation, blepharospasm, blindness, blindness transient, blindness unilateral, chalazion, choroiditis, colour blindness NOS, conjunctival cyst, corneal disorder NOS, corneal oedema, cyanopsia, cycloplegia, extraocular muscle paresis, eye disorder NOS, eye haemorrhage NOS, eye inflammation NOS, eyelid disorder NOS, glaucoma NOS, iridocyclitis, iris adhesions, iris cyst, keratitis, macular hole, madarosis, miosis, myopia aggravated, photopsia, pupillary light reflex tests abnormal, retinal detachment, retinal disorder, retinal haemorrhage, retinal vein occlusion, rubeosis iridis, vitreous haemorrhage	dacryostenosis acquired, eye discharge, eye inflammation, eyelid disorder, eyelid margin crusting, keratoconjunctivitis sicca, keratopathy, lid margin discharge, optic nerve disorder, scleral discolouration,
<i>Ear and labyrinth disorders</i>	ear pain, hypoacusis, tinnitus, vertigo	vertigo
<i>Cardiac disorders</i>	angina pectoris, arrhythmia, atrioventricular block NOS, bradycardia NOS, cardiac arrest, cardiac disorder NOS, cardiac failure NOS, cyanosis, extrasystoles NOS, myocardial infarction, palpitations, palpitations, tachycardia NOS, ventricular tachycardia	bradycardia, cardiac failure
<i>Vascular disorders</i>	arterial pressure NOS decreased, circulatory collapse, flushing,	flushing, hot flush

	hypertensive crisis	
<i>Respiratory, thoracic and mediastinal disorders</i>	asthma aggravated, chronic obstructive airways disease exacerbated, dry throat, dyspnoea exacerbated, epistaxis, expectoration, nasal congestion, nasal dryness, oropharyngeal swelling, pharyngolaryngeal pain	apnoea, increased upper airway secretion, respiratory disorder
<i>Gastrointestinal disorders</i>	abdominal pain, chapped lips, diarrhoea NOS, dyspepsia, gastric function disorder NOS, gastrointestinal disorder, gastrointestinal upset, mouth haemorrhage, nausea, vomiting	
<i>Hepatobiliary disorders</i>	autoimmune hepatitis	
<i>Skin and subcutaneous tissue disorders</i>	alopecia, angioneurotic oedema, cold sweat, dry skin, eczema NOS, eczema weeping, erythema, hair colour changes, hyperhidrosis, localised skin reaction, photosensitivity reaction, prurigo, pruritus, pruritus generalized, rash NOS, skin depigmentation, skin disorder, skin reaction, skin tightness, sweating increased, trichiasis, urticaria NOS	dermatitis, dermatitis exfoliative, dry skin, eczema, erythema, lichenification, periorbital oedema, pruritus, psoriasis, rash macular, scab, skin disorder, skin irritation
<i>Musculoskeletal and connective tissue disorders</i>	arthralgia, back pain, limb discomfort NOS, neck pain, pain in jaw, tendon disorder NOS	
<i>Renal and urinary disorders</i>	anuria, haematuria, incontinence NOS, micturition frequency decreased, pollakiuria, urine flow decreased	
<i>Reproductive system and breast disorders</i>	benign prostatic hyperplasia, breast mass NOS, erectile dysfunction NOS, peyronie's disease, priapism	menorrhagia
<i>Congenital, familial and genetic disorders</i>	coloboma , epidermal naevus	
<i>General disorders and administration site conditions</i>	asthenia, chest discomfort, chest pain, chest pressure sensation, condition aggravated, drug ineffective, facial pain, fall, fatigue, feeling abnormal, feeling hot, influenza like illness, lethargy, malaise, no adverse drug effect, oedema peripheral, pain	chest discomfort, drug ineffective, fatigue, unevaluable event
<i>Investigations</i>	arterial pressure NOS increased, blood bilirubin increased, blood cholesterol increased, heart rate abnormal, heart rate increased, intraocular pressure increased, liver function test abnormal, prostatic specific antigen increased, retinogram abnormal, serum ferritin increased, transferrin increased, weight decreased	heart rate increased, intraocular pressure increased

<i>Injury, poisoning and procedural complications</i>	accident NOS, accidental overdose, corneal injury NOS, face injury, head injury, injury	Excoriation
<i>Surgical and medical procedures</i>	cardiac pacemaker insertion	

Adverse drug reactions coded using MedDRA version 8.0

SOC = System Organ Class

PT = Preferred term

## **SYMPTOMS AND TREATMENT OF OVERDOSAGE**

There are no human data available on overdosage with *DuoTrav* (travoprost/timolol) Ophthalmic Solution or TRAVATAN® (travoprost ophthalmic solution).

Symptoms of systemic timolol overdosage are: bradycardia, hypotension, bronchospasm, and cardiac arrest. If such symptoms occur, treatment should be symptomatic and supportive.

Specific therapeutic measures for the treatment of overdosage with timolol maleate are reproduced below for ease of reference.

Gastric Lavage: If ingested.

Symptomatic bradycardia: Use atropine sulfate intravenously in a dosage of 0.25 to 2 mg to induce vagal blockade. If bradycardia persists, intravenous isoproterenol hydrochloride should be administered cautiously. In refractory cases the use of transvenous cardiac pacemaker may be considered.

Hypotension: Use sympathomimetic pressor drug therapy, such as dopamine, dobutamine or levarterenol. In refractory cases the use of glucagons hydrochloride has been reported to be useful.

Bronchospasm: Use isoproterenol hydrochloride. Additional therapy with aminophylline may be considered.

Acute cardiac failure: Conventional therapy with digitalis, diuretics and oxygen should be instituted immediately. In refractory cases the use of intravenous aminophylline is suggested. This may be followed if necessary by glucagon hydrochloride which as been reported to be useful.

Heart block (second or third degree): Use isoproterenol hydrochloride or a transvenous cardiac pacemaker.

### **DOSAGE AND ADMINISTRATION**

The recommended dosage is one drop in the affected eye(s) once-daily in the morning. The dosage of *DuoTrav* (travoprost/timolol) Ophthalmic Solution should not exceed once-daily since it has been shown that more frequent administration of prostaglandin analogues may decrease the intraocular pressure lowering effect. If one dose is missed, treatment should continue with the next dose as normal.

The use of *DuoTrav* may be considered in patients who require both timolol and travoprost. If more than one topical ophthalmic drug is being used, the drugs should be administered at least five minutes apart.

## PHARMACEUTICAL INFORMATION

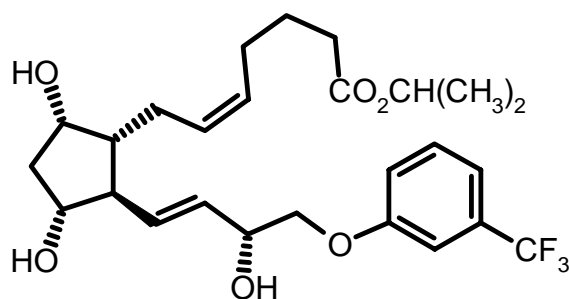
*DuoTrav* (travoprost/timolol) Ophthalmic Solution is a combination of a topical prostaglandin analogue and a topical beta-adrenergic receptor blocking agent.

### Drug Substance

Common Name: Travoprost

Chemical Name: [1R-[1 $\alpha$ (Z),2 $\beta$ (1E,3R\*),3 $\alpha$ ,5 $\alpha$ ]]-7-[3,5-Dihydroxy-2-[3-hydroxy-4-[3-(trifluoromethyl)phenoxy]-1-butenyl]cyclopentyl]-5-heptenoic acid, 1-methylethyl ester

Structural Formula:



Molecular Formula: C<sub>26</sub>H<sub>35</sub>F<sub>3</sub>O<sub>6</sub>.

Molecular Weight: 500.56

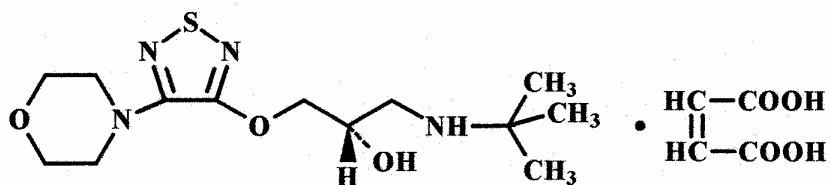
Description: Travoprost is a clear, colourless to pale yellow oil.

Solubility: Very soluble in acetonitrile, methanol, octanol, and chloroform. Practically insoluble in water.

Common Name: Timolol maleate

Chemical Name: (-)-1-(*tert*-Butylamino)-3-[(4-morpholino-1,2,5-thiadiazol-3-yl)oxy]-2-

Structural Formula:



Molecular Formula:  $C_{13}H_{24}N_4O_3S \cdot C_4H_4O_4$

Molecular Weight: 432.49

Description: Timolol maleate is a white, odorless, crystalline powder.

Solubility: Soluble in water, methanol, and alcohol.

### Composition

*DuoTrav* (travoprost/timolol) Ophthalmic Solution is a sterile, isotonic, buffered, preserved, aqueous solution of travoprost 0.04 mg/mL and timolol maleate 6.8 mg/mL (equivalent to 5 mg timolol base) supplied in the Alcon DROP-TAINER® package system.

Each mL contains 0.04 mg travoprost and 6.8 mg timolol maleate. Preservative: benzalkonium chloride. Inactive Ingredients: mannitol, tromethamine, polyoxyl 40 hydrogenated castor oil, boric acid, edetate disodium, hydrochloric acid and purified water.

### Stability and Storage Recommendations

Store at 2° – 25° C. No refrigeration required.

## AVAILABILITY OF DOSAGE FORMS

*DuoTrav* (travoprost/timolol) Ophthalmic Solution is a sterile, isotonic, buffered, preserved, aqueous solution of travoprost and timolol maleate supplied in the Alcon DROP-TAINER® package system. This package system comprises a white, opaque, polypropylene dispenser

bottle with a natural polypropylene dropper tip and a dark blue polypropylene closure. Tamper evidence is provided with a neck-band which shrinks to conform around the closure and neck area of the package.

*DuoTrav* is supplied as 2.5 mL solution in a 4 mL bottle or 5 mL solution in a 7.5 mL bottle.

A 2.5 mL bottle of *DuoTrav* contains at least 94 drops of solution.

## INFORMATION FOR THE CONSUMER

### Pr *DuoTrav* Ophthalmic Solution

Fixed combination of 0.04 mg/mL travoprost and 5 mg/mL timolol as timolol maleate

**Read all of this information carefully before you start taking/using this medicine.**

- *Read this leaflet carefully because it contains important information for you.*
- *If you have further questions, please ask your doctor or your pharmacist.*
- *This medicine has been prescribed for you personally. Never give it to anyone else. It may harm them, even if their symptoms are the same as yours.*
- *Keep this information. You may need to read it again.*

### *DuoTrav* SOLUTION AND OTHER MEDICINES

Please tell your doctor or pharmacist if you are taking (or recently took) any other medicines. Remember to mention also medicines that you bought without prescription, over-the-counter.

### WHAT MEDICATION HAS BEEN PRESCRIBED?

*DuoTrav* is a solution for use in the eyes only. *DuoTrav* Solution is a combination of two drugs that lower the pressure in the eye: travoprost (a prostaglandin) that increases the flow of fluid out of the eye and timolol (a beta-blocker) that decreases the amount of fluid produced by the eye.

## **WHAT IS *DuoTrav* SOLUTION USED FOR?**

*DuoTrav* Solution is used to lower the pressure in your eye(s). Increased pressure in the eye(s) is found in patients who have open-angle glaucoma or ocular hypertension. If left untreated, the increased pressure can lead to nerve damage within the eye ultimately affecting eyesight.

## **WHAT DOES *DuoTrav* SOLUTION CONTAIN AND HOW IS IT SUPPLIED?**

*DuoTrav* Solution contains 0.04 mg/mL of travoprost and 5 mg/mL of timolol (as timolol maleate). It also contains benzalkonium chloride (a preservative), mannitol, tromethamine, polyoxyl 40 hydrogenated castor oil, boric acid, edetate disodium, hydrochloric acid and purified water.

*DuoTrav* Solution is supplied as 2.5 mL solution in a 4 mL bottle or 5 mL solution in a 7.5 mL bottle.

## **WHEN *DuoTrav* SOLUTION SHOULD NOT BE USED**

**Do not use *DuoTrav* Solution if:**

- **you have, or have ever had, an unusual or allergic reaction to the medicinal and other ingredients in *DuoTrav* Solution (See WHAT DOES *DuoTrav* CONTAIN AND HOW IS IT SUPPLIED?)**
- **you have, or have had, a lung condition such as asthma or chronic obstructive pulmonary disease (COPD)**
- **you have a heart condition or heart disease**

## **TALK TO YOUR DOCTOR BEFORE USING *DuoTrav* SOLUTION IF:**

- **you have diabetes, low blood sugar, thyroid condition or kidney problems**
- **you have muscle weakness or have been diagnosed with myasthenia gravis**
- **you have problems with blood circulation to the brain**
- **you are pregnant, planning to become pregnant, or breastfeeding**
- **you are planning to have surgery**

- **you are using any other eye drops, or taking any other prescription or nonprescription drugs, especially if you are taking medicine to lower blood pressure or to treat heart disease.**

#### **WARNINGS AND PRECAUTIONS**

- **Do not drive if you experience blurred vision or eye discomfort after using *DuoTrav* Solution**
- **Do not touch dropper tip to eyelids, surrounding tissues, or to any surface, to avoid contamination**
- **Do not use while wearing contact lenses. *DuoTrav* Solution contains the preservative, benzalkonium chloride, which may be absorbed by contact lenses. You should remove your contact lenses before using your eye drops. Wait 15 minutes after using *DuoTrav* Solution before reinserting your lenses.**
- **Not recommended to individuals under 18 years of age**

#### **ARE THERE SPECIAL CONSIDERATIONS FOR PATIENTS OVER 65 YEARS OF AGE?**

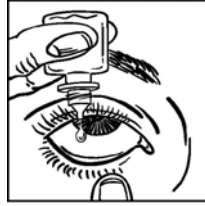
*DuoTrav* Solution can be used safely in patients over 65 years of age.

#### **HOW DO I USE *DuoTrav* SOLUTION?**

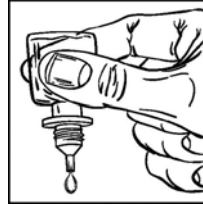
Adults - Use one drop of *DuoTrav* Solution in the affected eye(s) once daily (in the morning).

If you miss a dose of this medicine, wait until it is time for your next dose. Do not double doses. If the drop misses your eye, wipe with a tissue and try again.

To keep the dropper tip and solution clean, be careful not to touch the eyelids or surrounding areas with the dropper tip of the bottle. Keep the bottle tightly closed when not in use.



1



2

- Get the bottle of *DuoTrav* Solution and a mirror.
- Wash your hands.
- If you wear contact lenses, remove them before using your eye drops.
- Open the bottle being careful not to touch the dropper tip. Hold the bottle, pointing down, between your thumb and fingers.
- Tilt your head back. Pull down your eyelid with a clean finger, until there is a 'pocket' between the eyelid and your eye. The drop will go in there (see Picture 1).
- Bring the bottle tip close to the eye. Use the mirror if it helps.
- Don't touch your eye or eyelid, surrounding areas or other surfaces with the bottle tip. It could contaminate the drops.
- Gently squeeze the bottle to release one drop of *DuoTrav* Solution (see Picture 2).
- If you take drops in both eyes, repeat the steps for your other eye.
- Put the bottle cap back on tightly after use.

If you are using more than one type of medication in your eyes, wait at least 5 minutes between each different medication.

### **WHAT DO I DO IF I TAKE TOO MUCH *DuoTrav* SOLUTION?**

If you put too much *DuoTrav* Solution in your eye(s), rinse it all out with warm tap water. Using too many drops may cause your eyes to become red and irritated. Don't put in any more drops until it's time for your next regular dose.

If *DuoTrav* Solution is accidentally taken by mouth or injected, contact your doctor or pharmacist for advice.

## WHAT SIDE EFFECTS MIGHT I HAVE WITH *DuoTrav* SOLUTION?

- *DuoTrav* Solution may increase the length, thickness, colour and/or number of your eyelashes. A small number of people may notice their eye lid skin looks darker after using *DuoTrav* Solution for some time.
- *DuoTrav* Solution may change the colour of your eye. It may make your iris (the coloured part of your eye) more brown. This effect may be more noticeable in patients with eye colours that are mixtures of green and brown, blue/gray and brown, or yellow and brown. The brown pigment may gradually spread outward toward the outside edge of the iris. However, the entire iris or parts of it may become more brownish in appearance.
- If you use *DuoTrav* Solution in one eye only, the possible changes described above may appear **in the treated eye only**. Therefore, there is potential for permanent difference in the colour between the treated and untreated eyes. Your doctor will examine you regularly to make sure that your medication is working and look for changes in eye colour. If you should experience any changes in eye colour, your doctor can stop treatment. However, any colour change that has already occurred may be permanent, even after the medication is stopped.

Some people who use *DuoTrav* Solution may get side effects. They can be unpleasant, but most of them soon pass. You can usually keep taking the drops, unless the effects are serious. If you're worried, talk to your doctor or pharmacist.

While using *DuoTrav* Solution you may experience some or all of the following reactions in your eye: redness, itching, dryness, pain, sensitivity to light, abnormal sensation in eye or other eye irritations, blurred vision, temporary reduction of vision, tearing, growth of eyelashes, eye swelling. You may also experience discomfort (burning and stinging), changes in vision and itching, swollen, heavy, painful or irritated eyelids.

You may also experience reactions in other areas of your body, including: headache, postnasal drip, thirst, cough or throat irritation, a change in blood pressure or heart rate, disturbance in attention, dizziness, nervousness, skin infection or irritation, skin redness, ear infections, pain in

arms or legs, shortness of breath, difficulty breathing, increased eye pressure, a change in urine color or an allergic reaction following administration of the drops.

Other side effects not listed above may also occur in some patients.

If you notice any undesirable effects not mentioned in this information, you should stop using *DuoTrav* Solution and call your doctor or pharmacist immediately and follow his/her advice.

**YOU SHOULD TALK TO YOUR DOCTOR ABOUT DISCONTINUING USE OF *DuoTrav* SOLUTION IF:**

- you develop an eye or eyelid infection
- you injure your eye(s)
- you plan to have surgery on your eye(s)
- you develop any hypersensitivity reaction to the product such as swelling or inflammation of the eye(s) or eyelid(s)

**HOW LONG CAN I KEEP, AND HOW LONG SHOULD I STORE, *DuoTrav* SOLUTION?**

Keep these eye drops in a safe place out of the reach and sight of children.

Store between 2°C and 25°C. No refrigeration is required.

Do not use this medicine after the expiry date on the bottle or carton.

**FURTHER INFORMATION**

Contact your doctor or pharmacist.

## PHARMACOLOGY

### Animal Pharmacology

No non-clinical ocular or systemic pharmacology studies were conducted on Travoprost/Timolol Ophthalmic Solution (0.004% / 0.5% w/v) since the pharmacology of each has been well established previously in the medical and scientific literature. Previous studies have shown that the concomitant application of FP agonists with timolol results in an additional reduction in IOP compared to the administration of either single agent (5-10).

### Clinical Pharmacology

#### Human Pharmacodynamics

The active components of *DuoTrav* Solution, travoprost and timolol maleate, are approved therapeutic agents for the reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension, with different mechanisms of action. *DuoTrav* Solution produces greater mean IOP reductions than those produced by either TRAVATAN (travoprost ophthalmic solution) or Timolol Ophthalmic Solution, 0.5% used alone.

#### Human Pharmacokinetics

A single-centre, double-masked, randomized, 3-way crossover, multiple-dose safety and pharmacokinetic study was conducted to determine the plasma concentrations of travoprost free acid and timolol, when a single drop of *DuoTrav* Solution was administered compared to the plasma concentrations of travoprost free acid and timolol when TRAVATAN and Timolol Ophthalmic Solution, 0.5% were administered independently, once-daily, in the morning, for 3 days. Pharmacokinetic parameters of travoprost free acid were not estimated due to low systemic exposure and a limited number of quantifiable plasma samples. There was no apparent accumulation of travoprost free acid based on the observation that plasma concentrations were consistent between Day 1 and Day 3 and similar for each group. Timolol concentrations were quantifiable in all subjects who received *DuoTrav* Solution or Timolol 0.5%. There were no statistically significant differences ( $p > 0.05$ ) in plasma concentrations of timolol between the two treatment groups at any time-point on either Day 1 or Day 3.

There were no statistically significant differences in timolol  $C_{\max}$ ,  $T_{\max}$  or  $AUC_{0-12}$  between the two treatment groups on either Day 1 or Day 3. The mean timolol  $C_{\max}$  estimates on Day 3 (steady-state) were 0.692 ng/mL for *DuoTrav* Solution and 0.613 ng/mL for Timolol 0.5%, resulting in a mean difference of 0.087 ng/mL in  $C_{\max}$ , which was not statistically significant, whereas timolol  $t_{1/2}$  estimates ( $4.2 \pm 1.6$  hours) on Day 3 was significantly shorter for the fixed combination than for timolol alone ( $4.7 \pm 1.4$  hours). There was no apparent accumulation of timolol based on similar concentration-time curves for Day 1 and Day 3.

The mean steady-state timolol  $C_{\max}$  ( $0.692 \pm 0.384$  ng/mL) observed following topical ocular administration of *DuoTrav* Solution was approximately 122-fold lower than the mean  $C_{\max}$  of  $84.3 \pm 33.8$  ng/mL reported in literature after a single 20-mg oral dose of timolol in healthy volunteers (11).

### **Clinical Trials**

Five multicenter, randomized, double-masked, parallel-group, controlled clinical trials were conducted to assess the clinical efficacy and safety of *DuoTrav* Solution.

One trial (C-02-03) compared *DuoTrav* Solution dosed once-daily, in the morning, to *DuoTrav* Solution dosed once-daily, in the evening, over a six-week period. To qualify for the study, patients had to be diagnosed with open-angle glaucoma or ocular hypertension and had to be currently treated with one or more IOP-lowering medications. The primary efficacy endpoint was an assessment of mean IOP at the 9 AM, 11 AM and 4 PM timepoints at Week 2 and Week 6. The two dosing regimens were to be declared equivalent if the confidence interval limits were within  $\pm 2.5$  mmHg. Safety assessments included visual acuity, ocular signs (cornea, iris/anterior chamber, lens, aqueous cells and flare), ocular hyperaemia, dilated fundus parameters (vitreous, retina/macula/choroid, optic nerve) and cardiovascular parameters (pulse rate, systolic and diastolic blood pressure).

Participants included 92 adult patients (87% with open-angle glaucoma, which could include a pigmentary or exfoliative component, and 13% with ocular hypertension) with a baseline mean IOP of 25 to 27 mmHg following washout from previous IOP-lowering therapy. The results of this study indicate that the IOP-lowering efficacy of *DuoTrav* Solution is independent of time of dosing (morning vs. evening), providing clinically relevant and equivalent IOP control throughout the day. All of the two-sided 95% confidence limits were within  $\pm 2.5$  mmHg. Mean IOP reductions ranged from approximately 8 to 10 mmHg, equating to IOP reductions of 32% to 38% relative to baseline.

The most frequent ocular adverse drug reactions to *DuoTrav* Solution in C-02-03 included ocular hyperaemia (6 patients; 13.0%) and ocular pruritus (4 patients; 4.3%). The most frequent non-ocular adverse drug reaction was hypertension, occurring in 2 patients (2.2%). All other non-ocular adverse drug reactions occurred in 1 patient each. No clinically relevant differences were noted comparing the safety of morning and evening dosing.

**Table 7: Mean IOP (mmHg) Comparison of Morning and Evening Dosing with *DuoTrav* Solution (Per Protocol Data Set – C-02-03)**

	Week 2			Week 6		
	9AM	11AM	4PM	9AM	11AM	4PM
<i>DuoTrav</i> Morning Dosing	16.6	16.6	16.6	16.7	16.7	16.5
<i>DuoTrav</i> Evening Dosing	17.2	16.7	16.1	17.0	16.9	16.3
Difference	-0.6 <sup>a</sup>	-0.1 <sup>a</sup>	0.5 <sup>a</sup>	-0.3 <sup>a</sup>	-0.2 <sup>a</sup>	0.2 <sup>a</sup>
Upper 95% Confidence Interval	0.9	1.3	2.0	1.1	1.3	1.7
Lower 95% Confidence Interval	-2.0	-1.6	-1.0	-1.8	-1.7	-1.2

<sup>a</sup> p-value > 0.05

A 3-month study (C-01-69) was designed to compare the safety and IOP-lowering efficacy of *DuoTrav* Solution to TRAVATAN (travoprost 0.004%) alone or to Timolol 0.5% alone. Patients enrolled could have been on previous IOP-lowering therapy or not on medication. The primary efficacy endpoint was an assessment of mean IOP at the 8 AM, 10 AM and 4 PM timepoints at Week 2, Week 6 and Month 3. A three-month, planned, masked extension included a visit at Month 6 for additional safety follow-up.

Safety assessments included visual acuity, ocular signs (cornea, iris/anterior chamber, lens, aqueous cells and flare), ocular hyperaemia, dilated fundus parameters (vitreous, retina/macula/choroid, optic nerve), iris/eyelash photography, cardiovascular parameters (pulse, systolic and diastolic blood pressures) and visual fields.

Participants included 263 adult and elderly patients with open-angle glaucoma (which could include a pigmentary or exfoliative component) (69%) or ocular hypertension (31%) with baseline mean IOPs, following washout from previous IOP-lowering therapy, if applicable, of 27 to 30 mmHg. The results of this study indicate that *DuoTrav* Solution produces statistically significant and clinically relevant reductions in IOP ranging from approximately 9 to 12 mmHg which equates to IOP reductions of 32% to 38% relative to baseline. IOP-lowering with *DuoTrav* Solution, dosed once-daily in the morning, was 2 to 3 mmHg greater than that of Timolol Ophthalmic Solution, 0.5%, dosed twice-daily, at all visits and times, and was 1 to 2 mmHg greater than that of TRAVATAN at all times of day. This is most evident at the crucial 8 AM timepoint when IOP is highest and is 24 hours post-dosing of the fixed combination. Due to its complementary mechanisms of action (increased uveoscleral outflow and suppression of aqueous humor production), *DuoTrav* Solution produces large mean IOP reductions in all demographic subgroups.

In this study where baseline IOPs were 27 to 30 mmHg, 50% of patients receiving *DuoTrav* achieved IOP below 18 mmHg on at least one timepoint for every visit.

In clinical practice, the appropriate value of a target IOP (an IOP level that would be considered a clinical success) is determined by the physician for each patient. Information from the recent Advanced Glaucoma Intervention Study (AGIS)(1) indicates that an IOP of less than 18 mmHg is correlated with reduced progression of visual field defects associated with glaucoma.

**Table 8: Mean IOP (mmHg) Comparison of *DuoTrav* and Timolol 0.5% and of *DuoTrav* and TRAVATAN (Intent-to-Treat Data Set – C-01-69)**

	Week 2			Week 6			Month 3		
	8AM	10AM	4PM	8AM	10AM	4PM	8AM	10AM	4PM
<i>DuoTrav</i>	18.9	18.1	17.5	18.9	17.9	18.2	18.7	18.4	18.5
Timolol 0.5%	21.3	20.4	20.2	20.6	20.0	19.8	20.8	19.9	20.1
Difference	-2.4 <sup>a</sup>	-2.2 <sup>a</sup>	-2.7 <sup>a</sup>	-1.7 <sup>a</sup>	-2.1 <sup>a</sup>	-1.7 <sup>a</sup>	-2.1 <sup>a</sup>	-1.5 <sup>a</sup>	-1.5 <sup>a</sup>
Upper 95% CI	-1.3	-1.1	-1.6	-0.5	-1.0	-0.6	-0.9	-0.4	-0.4
Lower 95% CI	-3.5	-3.3	-3.8	-2.8	-3.2	-2.8	-3.2	-2.6	-2.6
<i>DuoTrav</i>	18.9	18.1	17.5	18.9	17.9	18.2	18.7	18.4	18.5
TRAVATAN	20.5	18.9	18.7	20.3	19.2	18.7	20.5	19.3	18.9
Difference	-1.6 <sup>b</sup>	-0.8	-1.2 <sup>b</sup>	-1.4 <sup>b</sup>	-1.3 <sup>b</sup>	-0.5	-1.8 <sup>b</sup>	-1.0	-0.4
Upper 95% CI	-0.5	0.4	-0.0	-0.3	-0.1	0.6	-0.6	0.2	0.8
Lower 95% CI	-2.8	-1.9	-2.3	-2.5	-2.4	-1.6	-2.9	-2.1	-1.5

<sup>a</sup> p<0.05 *DuoTrav* vs. Timolol 0.5%

<sup>b</sup> p<0.05 *DuoTrav* vs. TRAVATAN

**Table 9: Percent of Patients with IOP < 18 mmHg on a Least One Timepoint at Every Visit (Intent-to-Treat Data Set – C-01-69)**

	Percent of Patients
DuoTrav	50%
TRAVATAN	29%
Timolol 0.5%	23%

The most frequent ocular adverse drug reactions with *DuoTrav* in C-01-69 included ocular hyperaemia (12 patients; 14.1%), ocular discomfort (6 patients; 7.1%), photophobia (4 patients; 4.7%), and changes in eyelash characteristics (4 patients; 4.7%). The most frequent non-ocular adverse drug reaction was headache, occurring in 2 patients (2.4%). All other non-ocular adverse drug reactions occurred in 1 patient each. No clinically relevant differences in safety were noted between the 3-month and 6-month data sets.

Two 3-month studies (C-01-70 and C-02-41) were designed to compare the IOP-lowering efficacy and safety of *DuoTrav* Solution to the concomitant administration of TRAVATAN and Timolol 0.5% in patients with open-angle glaucoma or ocular hypertension. Both studies were multicenter, double-masked, parallel group studies. The two treatment groups were: 1) *DuoTrav*

Solution dosed once-daily in the morning; and 2) Timolol 0.5% dosed once-daily in the morning plus TRAVATAN dosed once-daily in the evening. The dosing regimens were to be declared similar if the confidence interval limits were within  $\pm 1.5$  mmHg. In the second study (C-02-41), a third treatment group, Timolol 0.5% dosed twice daily, was also included. Patients enrolled could have been on previous IOP-lowering therapy or not on medication. The primary efficacy endpoint was an assessment of mean IOP at the 8 AM, 10 AM and 4 PM time points at Week 2, Week 6 and Month 3. A three-month, planned, masked extension included a visit at Month 6 for additional safety follow-up.

Safety assessments included visual acuity, ocular signs (cornea, iris/anterior chamber, lens, aqueous cells and flare), ocular hyperaemia, dilated fundus parameters (vitreous, retina/macula/choroid, optic nerve), iris/eyelash photography, cardiovascular parameters (pulse, systolic and diastolic blood pressures) and visual fields.

Participants included 316 (in C-01-70) and 403 (in C-02-41) adult and elderly patients with open-angle glaucoma, which could include a pigmentary or exfoliative component, (68% in C-01-70; 57% in C-02-41) or ocular hypertension (32% in C-01-70; 43% in C-02-41) with baseline mean IOPs, following washout from previous IOP-lowering therapy, if applicable, of 23 to 26 mmHg. The results of both studies indicate that *DuoTrav* Ophthalmic Solution produces IOP-lowering that is similar to the concomitant administration of TRAVATAN and Timolol 0.5% Ophthalmic Solutions and greater than Timolol 0.5% dosed twice-daily. Treatment-group differences in mean IOP were similar in the two studies and ranged from 0.1 to 1.1 mmHg, demonstrating the similarity of IOP reduction (see Tables 10, 11 and 12).

**Table 10: Mean IOP (mmHg) Comparison of *DuoTrav* and TRAVATAN + Timolol 0.5% for Test of Non-Inferiority (Per Protocol Dataset -- C-01-70)**

	Week 2			Week 6			Month 3		
	8AM	10AM	4PM	8AM	10AM	4PM	8AM	10AM	4PM
<i>DuoTrav</i>	16.1	15.5	15.2	15.9	15.7	15.6	16.5	16.1	15.6
TRAVATAN + Timolol 0.5%	16.0	15.2	14.8	15.8	14.8	14.7	16.1	15.1	14.8
Difference	0.1	0.3	0.5	0.1	1.0 <sup>a</sup>	0.9 <sup>a</sup>	0.5	0.9 <sup>a</sup>	0.8 <sup>a</sup>
Upper 95% CI	0.7	0.9	1.1	0.7	1.6	1.5	1.1	1.6	1.5
Lower 95% CI	-0.5	-0.4	-0.2	-0.5	0.3	0.3	-0.2	0.3	0.2

<sup>a</sup> p<0.05 *DuoTrav* vs. TRAVATAN + Timolol 0.5%

**Table 11: Mean IOP (mmHg) Comparison of *DuoTrav* and TRAVATAN + Timolol 0.5% for Test of Non-Inferiority (Per Protocol Dataset -- C-02-41)**

	Week 2			Week 6			Month 3		
	8AM	10AM	4PM	8AM	10AM	4PM	8AM	10AM	4PM
<i>DuoTrav</i>	17.4	16.8	16.2	17.0	16.6	16.2	17.1	16.5	16.3
TRAVATAN + Timolol	16.8	15.7	15.4	16.6	15.5	15.4	16.7	15.8	15.5
Difference	0.6	1.1 <sup>a</sup>	0.8 <sup>a</sup>	0.4	1.0 <sup>a</sup>	0.7 <sup>a</sup>	0.4	0.7	0.8 <sup>a</sup>
Upper 95% CI	1.3	1.8	1.5	1.1	1.7	1.5	1.2	1.4	1.6
Lower 95% CI	-0.1	0.4	0.0	-0.4	0.3	0.0	-0.3	-0.1	0.1

<sup>a</sup> p<0.05 *DuoTrav* vs. TRAVATAN + Timolol

**Table 12: Mean IOP (mmHg) Comparison of *DuoTrav* and Timolol 0.5% for Test of Superiority (Intent-to-Treat Dataset -- C-02-41)**

	Week 2			Week 6			Month 3		
	8AM	10AM	4PM	8AM	10AM	4PM	8AM	10AM	4PM
<i>DuoTrav</i>	17.5	16.8	16.2	17.0	16.6	16.2	17.2	16.5	16.4
Timolol 0.5%	18.3	18.0	18.3	18.8	17.9	17.9	18.8	17.8	17.5
Difference	-0.9 <sup>a</sup>	-1.3 <sup>a</sup>	-2.1 <sup>a</sup>	-1.8 <sup>a</sup>	-1.3 <sup>a</sup>	-1.7 <sup>a</sup>	-1.6 <sup>a</sup>	-1.3 <sup>a</sup>	-1.2 <sup>a</sup>
Upper 95% CI	-0.0	-0.4	-1.3	-0.9	-0.4	-0.8	-0.7	-0.5	-0.3
Lower 95% CI	-1.7	-2.1	-3.0	-2.7	-2.2	-2.6	-2.4	-2.2	-2.0

<sup>a</sup> p<0.05 *DuoTrav* versus Timolol 0.5%

In these studies where baseline IOPs were 23 to 26 mmHg, approximately 74% of patients receiving *DuoTrav* achieved IOP below 18 mmHg on at least one time point at every visit.

**Table 13: Percent of Patients with IOP < 18 mmHg  
on at Least One Timepoint at Every Visit  
(Intent-to-Treat Data Sets – C-01-70 and C-02-41)**

	Percent of Patients		
	C-01-70	C-02-41	Pooled
DuoTrav	79%	70%	74%
TRAVATAN + Timolol 0.5%	84%	80%	82%
Timolol 0.5%	---	52%	---

The most frequent ocular adverse drug reactions with *DuoTrav* in C-01-70 included ocular hyperaemia (20 patients; 12.4%), ocular discomfort (9 patients; 5.6%), ocular pruritus (6 patients; 3.7%), ocular dryness (5 patients; 3.1%), corneal staining (4 patients; 2.5%), keratitis (3 patients; 1.9%), ocular allergic reaction (3 patients; 1.9%), and ocular pain (3 patients; 1.9%).

The most frequent non-ocular adverse drug reaction was headache, occurring in 2 patients (1.2%). All other non-ocular adverse drug reactions (contact dermatitis, increased cough and skin discolouration) occurred in 1 patient each (0.6%).

The most frequent ocular adverse drug reactions with *DuoTrav* in C-02-41 included ocular hyperaemia (23 patients; 14.3%), ocular discomfort (20 patients; 12.4%), foreign body sensation (11 patients; 6.8%), ocular pruritus (7 patients; 4.3%), ocular dryness (5 patients; 3.1%), cells (4 patients; 2.5%), blurred vision (3 patients; 1.9%), lid erythema (3 patients; 1.9%), ocular pain (3 patients; 1.9%), and photophobia (3 patients; 1.9%). All non-ocular adverse drug reactions (abnormal urine, dyspnea, irritation throat, SGOT increased, SGPT increased and skin discolouration) occurred in 1 patient each (0.6%).

An analysis of the 6-month safety data from both C-01-70 and C-02-41 confirmed that *DuoTrav* has an acceptable safety profile with no clinically relevant differences noted between the 3-month and 6-month safety results.

In all 3-month studies, patients treated with *DuoTrav* Solution achieve sustainable IOP reduction after 2 weeks of therapy and the IOP reduction is maintained for 3 months.

No overall differences in safety or effectiveness have been observed between elderly and other adult patients.

The long-term safety of *DuoTrav* Ophthalmic Solution was evaluated in a 12-month study (C-02-28) comparing *DuoTrav* and XALACOM (latanoprost 0.005% / timolol 0.5% ophthalmic solution) in 407 patients with open-angle glaucoma or ocular hypertension. Safety assessments included visual acuity, ocular signs (cornea, iris/anterior chamber, lens, aqueous cells and flare), ocular hyperaemia, dilated fundus parameters (vitreous, retina/macula/choroid, optic nerve), iris/eyelash photography, cardiovascular parameters (pulse, systolic and diastolic blood pressures) and visual fields.

The most frequent ocular adverse drug reactions with *DuoTrav* in C-02-28 included ocular hyperaemia (31 patients; 15.0%), ocular pruritus (14 patients; 6.8%), ocular discomfort (9 patients; 4.3%), changes in eyelash characteristics (5 patients; 2.4%), ocular dryness (4 patients; 1.9%), and ocular pain (3 patients; 1.4%). Increased iris pigmentation occurred at an incidence of 2.4% (4 patients) (see Table 3 in the **ADVERSE REACTIONS** section). The most frequent non-ocular adverse drug reaction was skin discolouration, occurring in 2 patients (1.0%). All other non-ocular adverse drug reactions (allergy, asthma, dizziness, dyspnea, hypertension and increased cough) occurred in 1 patient each (0.5%).

An analysis of the safety data obtained across all studies indicates that *DuoTrav* is well tolerated with a safety profile similar to that obtained with the concomitant dosing of TRAVATAN and Timolol 0.5%. Studies conducted with the individual components of *DuoTrav* Solution indicate that the IOP-lowering effect of travoprost (14) and of timolol (15) are well maintained over a period of one year. Adverse drug reactions with *DuoTrav* Ophthalmic Solution were consistent

with those reported previously with TRAVATAN (travoprost ophthalmic solution) 0.004% and/or timolol maleate ophthalmic solution, 0.5%.

A summary of all ocular and non-ocular adverse drug reactions from all 5 multicenter clinical trials is presented in Table 2 in the **ADVERSE REACTIONS section**.

## **TOXICOLOGY**

### **SINGLE DOSE TOXICITY**

#### **Travoprost/Timolol Combination**

A one-day ocular irritation and comfort study with Travoprost/Timolol Ophthalmic Solution (0.004% / 0.5% w/v) in rabbits, dosed two drops to the right eye every 30 minutes for 10 doses, has revealed only moderate conjunctival congestion and minimal discomfort, comparable with the individual active components. Systemic single dose studies were not conducted with the combined drugs.

A 7.5 mL bottle of *DuoTrav* (40 µg/mL travoprost with 5 mg/mL timolol) contains 0.3 mg travoprost and 37.5 mg timolol. Exposure to the entire contents of a container by a 10 kg child would result in exposure of 0.03 mg/kg travoprost and 3.75 mg/kg timolol. The poor oral bioavailability of travoprost mitigates the hazard of accidental ingestion. Timolol is orally bioavailable, but has a low order of toxicity (mouse/rat oral LD<sub>50</sub> ~ 1000 mg/kg).

#### **Travoprost**

Travoprost was demonstrated to have a low order of acute toxicity. No LD<sub>50</sub> of travoprost has been established. No mortalities occurred in rats administered travoprost intravenously at a dose of 10 mg/kg (250,000-times the proposed clinical exposure) or in mice given up to 100 mg/kg/day (2,500,000-times the proposed clinical exposure). The most frequent clinical observations were discoloured urine and red material around the nose in rats, and lethargy and diarrhea in mice.

Administration of travoprost ophthalmic solution, up to 0.01%, two drops every half-hour for five or six hours, did not result any significant ocular or systemic effects.

### **Timolol**

Acute oral dosing studies established an LD<sub>50</sub> of approximately 1000 mg/kg for mice and rats. The most frequent clinical observations were decreased activity and bradypnea. Oral acute interaction studies in mice in which timolol maleate was administered with probenecid, methyldopa, hydralazine, hydrochlorothiazide, or tolbutamide, showed that these drugs had no effect on the toxicity of timolol maleate. Timolol maleate had no effect on hypoprothrombinemia induced by bishydroxycoumarin in the dog.

### **REPEATED DOSE TOXICITY**

#### **Travoprost/Timolol Combination**

Studies conducted to evaluate the potential ocular and systemic effects of the Travoprost/Timolol Solution consisted of two repeated-dose topical ocular studies, a 3-month rabbit study (with a 6-week interim analysis) and a 9-month rabbit study.

**Table 14: Repeated Dose Toxicity Studies with Travoprost/Timolol Ophthalmic Solution**

<b>Animal species, family</b>	<b>Number of animals/groups</b>	<b>Concentration (%)</b>	<b>Dosing method</b>	<b>Dosing period</b>	<b>Results</b>
Rabbit, pigmented	8/sex (3/sex were euthanized at 6 weeks)	Vehicle-control Travoprost 0.004%/Timolol 0.5% Travoprost 0.02%/Timolol 0.5% Travoprost 0.02%	One drop in the right eye, 3 times daily	3 months (interim analysis at 6 weeks)	No significant ocular or systemic toxicity
Rabbit, pigmented	6/sex	Vehicle-control Travoprost 0.004%/Timolol 0.5% Travoprost 0.02%/Timolol 0.5% Travoprost 0.02% Timolol 0.5%	One drop in the right eye, 3 times daily	9 months	No significant ocular or systemic toxicity

The nonclinical dosing regimen was 3-times and 15-times the clinical dose for timolol and travoprost, respectively.

In both studies, thorough ocular evaluations, consisting of biomicroscopic slit lamp examinations, indirect ophthalmic examinations, corneal pachymetry, intraocular pressure (IOP) measurements and specular microscopy of the corneal endothelium (9-month study only), revealed no significant ocular effects even with chronic administration at these doses. Systemic evaluations, including physical examinations, body weight measurements and clinical pathology evaluations, gross and microscopic pathology, likewise demonstrated no significant toxicity.

Maximum mean plasma travoprost free-acid and timolol concentrations at the end of 9 months treatment were  $0.509 \pm 0.231$  ng/mL travoprost and  $6.06 \pm 0.68$  ng/mL timolol, for the 0.02% travoprost/0.5% timolol group. These concentrations were similar to groups receiving the single entities. The results showed that the systemic exposure to both drugs which was not significantly altered by the concomitant administration. The mean plasma levels of travoprost free-acid in these rabbit studies were substantially higher than those measured in clinical subjects for either drug, demonstrating good exposure-based safety margins.

No chronic studies of greater than 9 months duration were conducted with Travoprost/Timolol fixed Combination.

### **Travoprost**

Topical ocular administration of travoprost ophthalmic solution, 0.01%, three times a day for six months, in rabbits, resulted in no significant ocular or systemic effects. Iris pigmentation and a species specific increase in palpebral fissure and increase in lid retraction was observed in some monkeys receiving 0.0015%, 0.004% or 0.012% travoprost ophthalmic solution for up to one year. No other significant ocular or systemic effects were seen.

The increased iridial pigmentation observed in monkeys and also in humans during chronic ocular treatment with travoprost is considered to be a class effect of prostaglandins. It is of particular interest that naturally occurring prostaglandins such as  $\text{PGF}_{2\alpha}$  and  $\text{PGE}_2$  also cause increased pigmentation of the iris in cynomolgus monkeys. It should also be noted that both

cynomolgus monkey and human iridial melanocytes express FP receptors in their cell membrane, and since travoprost is a selective FP receptor agonist, it implies that the effect is mediated by FP receptors in the melanocytes.

Subchronic intravenous administration of travoprost in rats at all doses employed (100 to 1000 micrograms/kg/day) resulted in trace-to-moderate hyperostosis and bone fibrosis. Incidence and severity were dose related, and determined bone to be a target organ of toxicity in rats. Similar studies in mice resulted in no significant systemic effects at doses of up to 1000  $\mu\text{g}/\text{kg}/\text{day}$ .

Chronic systemic administration (subcutaneous) of travoprost to rats at doses of 30 and 100 micrograms/kg/day resulted in dose-related hyperostosis and bone fibrosis similar to that observed in the subchronic study. No effect was observed in bone at 10 micrograms/kg/day (250-times the proposed clinical exposure), which was considered the no effect level.

### **Timolol**

No adverse ocular effects were observed in rabbits and dogs administered Timolol Maleate Ophthalmic Solution topically in studies lasting one and two years, respectively.

Timolol was administered orally to rats at dose levels 5, 10 and 25 mg/kg/day for up to 67 weeks. No physical signs, ocular signs or deaths which could be attributed to the drug were evident.

In a 54 week oral study, timolol was administered to dogs at doses of 5, 10 and 25 mg/kg/day. Body weight and food consumption were normal and no physical signs attributable to treatment were evident. Slight focal hyperplasia of the transitional epithelium was seen in the renal pelvis of one dog receiving 25 mg/kg/day.

In rats treated with 100 to 400 mg/kg timolol maleate for seven weeks, excessive salivation seen 5 to 10 minutes after dosing has a dose related incidence in the first week of the study. At necropsy, organ weight studies revealed a significant increase in the kidneys, spleen and liver of

some treated animals. Except for splenic congestion, there were no morphological changes to account for the increase in organ weights. Rats treated with 1 gram per day for eight weeks exhibited ptilyamism, muscle tremors and transient pale extremities.

In dogs, doses of 200 mg/kg timolol maleate or higher, were lethal to some animals. Low grade tubular nephrosis and trace amounts of hyaline casts in the collecting and convoluted tubules occurred in one of two dogs administered 100 mg/kg/day and in both dogs receiving 400 mg/kg/day. Small foci of tubular degeneration and regeneration occurred in the nephrotic areas. Similar slight multi focal degeneration of the collecting tubules in the medulla of both kidneys was evident in one of four dogs in a 15 day intravenous toxicity study.

## **CARCINOGENESIS**

Two-year carcinogenicity studies in mice and rats at subcutaneous doses of 10, 30, or 100 µg/kg/day travoprost, did not show any evidence of carcinogenic potential. However, at 100 µg/kg/day, male rats were only treated for 82 weeks, and the maximum tolerated dose (MTD) was not reached in the mouse study. The high dose (100 µg/kg/day) corresponds to exposure levels over 400 times the human exposure at the maximum recommended human ocular dose (MRHOD), based on plasma active drug levels.

In a two-year study of timolol maleate administered orally to rats, there was a statistically significant increase in the incidence of adrenal pheochromocytomas in male rats administered 300 mg/kg/day (approximately 42,000 times the MRHOD). This was not observed in rats administered oral doses equivalent to approximately 14,000 times the MRHOD.

In a lifetime oral study of timolol maleate in mice, there were statistically significant increases in the incidence of benign and malignant pulmonary tumors, benign uterine polyps, and mammary adenocarcinomas in female mice at 500 mg/kg/day (approximately 71,000 times the MRHOD), but not at 5 or 50 mg/kg/day (approximately 700 or 7,000, respectively, times the MRHOD). In a subsequent study in female mice, in which postmortem examinations were limited to the uterus

and the lungs, a statistically significant increase in the incidence of pulmonary tumors was again observed at 500 mg/kg/day.

The increased occurrence of mammary adenocarcinomas was associated with elevations in serum prolactin, which occurred in female mice administered oral timolol at 500 mg/kg/day, but not at doses of 5 or 50 mg/kg/day. An increased incidence of mammary adenocarcinomas in rodents has been associated with administration of several other therapeutic agents that elevate serum prolactin, but no correlation between serum prolactin levels and mammary tumors has been established in humans. Furthermore, in adult human female subjects who received oral dosages of up to 60 mg of timolol maleate (the maximum recommended human oral dosage), there were no clinically meaningful changes in serum prolactin.

No carcinogenicity studies were conducted with Travoprost/Timolol fixed Combination Solution.

## **MUTAGENESIS**

Travoprost was not mutagenic in the Ames test, mouse micronucleus test and rat chromosome aberration assay. A slight increase in the mutant frequency was observed in one of two mouse lymphoma assays in the presence of rat S-9 activation enzymes.

Timolol maleate was devoid of mutagenic potential when tested in vivo (mouse) in the micronucleus test and cytogenetic assay (doses up to 800 mg/kg) and in vitro in a neoplastic cell transformation assay (up to 100 µg/mL). In Ames tests, the highest concentrations of timolol employed, 5,000 or 10,000 µg/plate, were associated with statistically significant elevations of revertants observed with tester strain TA 100 (in seven replicate assays), but not in the remaining three strains. In the assays with tester strain TA 100, no consistent dose response relationship was observed, and the ratio of test to control revertants did not reach 2. A ratio of 2 is usually considered the criterion for a positive Ames test.

No mutagenicity studies were conducted with Travoprost/Timolol fixed Combination Solution.

## **REPRODUCTION & TERATOLOGY**

Travoprost did not affect mating or fertility indices in male or female rats at subcutaneous doses up to 10 µg/kg/day [250 times the MRHOD of 0.04 µg/kg/day]. At 10 µg/kg/day, the mean number of corpora lutea was reduced, and the post-implantation losses were increased. These effects were not observed at 3 µg/kg/day (75 times the MRHOD).

Travoprost was teratogenic in rats, at an intravenous (IV) dose of 10 µg/kg/day (250 times the MRHOD), evidenced by an increase in the incidence of skeletal malformations as well as external and visceral malformations, such as fused sternebrae, domed head and hydrocephaly. Travoprost was not teratogenic in rats at IV doses up to 3 µg/kg/day (75 times the MRHOD), or in mice at subcutaneous doses up to 1.0 µg/kg/day (25 times the MRHOD). Travoprost produced an increase in post-implantation losses and a decrease in fetal viability in rats at IV doses > 3 µg/kg/day (75 times the MRHOD) and in mice at subcutaneous doses > 0.3 µg/kg/day (7.5 times the MRHOD).

In the offspring of female rats that received travoprost subcutaneously from Day 7 of pregnancy to lactation Day 21 at the doses of  $\geq 0.12$  µg/kg/day (3 times the MRHOD), the incidence of postnatal mortality was increased, and neonatal body weight gain was decreased. Neonatal development was also affected, evidenced by delayed eye opening, pinna detachment and preputial separation, and by decreased motor activity.

Reproduction and fertility studies with timolol maleate in rats demonstrated no adverse effect on male or female fertility at doses up to 21,000 times the MRHOD.

Teratogenicity studies with timolol in mice, rats, and rabbits at oral doses up to 50 mg/kg/day (7,000 times the MRHOD) demonstrated no evidence of fetal malformations. Although delayed fetal ossification was observed at this dose in rats, there were no adverse effects on postnatal development of offspring. Doses of 1000 mg/kg/day (142,000 times the MRHOD) were

maternotoxic in mice and resulted in an increased number of fetal resorptions. Increased fetal resorptions were also seen in rabbits at doses of 14,000 times the MRHOD, in this case without apparent maternotoxicity.

No reproduction or teratology studies were conducted with Travoprost/Timolol fixed Combination Solution.

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