PRODUCT MONOGRAPH

TRAVATAN®

Travoprost Ophthalmic Solution, 0.004% w/v
(with benzalkonium chloride, 0.015%)

TRAVATAN® Z

Travoprost Ophthalmic Solution, 0.004% w/v
(without benzalkonium chloride)

THERAPEUTIC CLASSIFICATION:

Elevated Intraocular Pressure Therapy
Prostaglandin $F_{2\alpha}$ analogue

Alcon Canada Inc
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ACTIONS & CLINICAL PHARMACOLOGY

Mechanism of Action

Travoprost, an isopropyl ester prodrug, is rapidly hydrolyzed by esterases in the cornea to the biologically active free acid. Travoprost free acid is a highly selective, potent agonist for the FP prostanoid receptor. FP receptor agonists are thought to reduce intraocular pressure (IOP) by increasing the outflow of aqueous humor, primarily by increased uveoscleral outflow.

Pharmacokinetics/ Pharmacodynamics

TRAVATAN® (travoprost) Ophthalmic Solution, when applied topically to the eye, reduces 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 is absorbed through the cornea. Studies in rabbits have shown peak concentrations in aqueous humor were reached one to two hours following topical administration. In humans, peak plasma concentrations of travoprost free acid were low (25 pg/mL or less) and occurred within 30 minutes following topical ocular administration of one drop of 0.004% travoprost ophthalmic solution.

Distribution: Travoprost free acid is moderately distributed into body tissues with a volume of distribution of 2.6 L/kg in rats. Radioactivity levels in rat tissues following a single subcutaneous dose of ^{14}C-travoprost dropped rapidly during the first 3 hours and by 24 hours were below or near detection limits (<0.2 - 6 ng equiv./g). Binding of travoprost free acid to plasma proteins is moderate at 80% and linear over a 10,000-fold concentration range (0.10 - 100 ng/mL).

Metabolism: Metabolism was studied in rats, dogs and monkeys. Systemically, travoprost free acid is rapidly and extensively metabolized in the kidney, liver and lung to inactive metabolites. Biotransformations include beta-oxidation of the α(carboxylic acid) chain to give the 1,2-dinor and 1,2,3,4-tetranor analogs, oxidation of the 15-hydroxyl moiety, as well as reduction of the 13,14 double bond.

Excretion: In rats, 95% of a subcutaneous radiolabeled dose was eliminated within 24 hours. The major route of elimination was via the bile (61%) with the remainder excreted by the kidneys. In humans, elimination from plasma was rapid resulting in concentrations below the limit of quantitation (< 10 pg/mL) by one hour.

Clinical Studies

In three controlled clinical studies, with durations from 6 to 12 months, patients with open-angle glaucoma or ocular hypertension were treated once daily in the evening with TRAVATAN® Solution 0.004%. TRAVATAN® Solution reduced IOP 6.7 to 9.0 mmHg. Stable diurnal IOP reductions were achieved as early as 2 weeks after initiation of therapy and were maintained over the 6 to 12 month treatment period.

In a multi-center, randomized, controlled trial, patients with mean baseline intraocular pressure of 24-26 mmHg on TIMOPTIC* 0.5% BID, who were treated with TRAVATAN® Solution 0.004% dosed QD adjunctively to TIMOPTIC* 0.5% BID, demonstrated 6-7 mmHg additional reductions in intraocular pressure.

There are no plasma interactions with the concomitant administration of travoprost and timolol.

Summary of patient demographics for clinical trials in specific indication.

Study #	Trial design	Dosage, route of administration and duration	Study subjects	Mean age (Range)	Gender
1 - C-97-71	Randomised, triple masked, multicentre, parallel group, active control in patients with open-angle glaucoma or ocular hypertension.	1 drop QD of placebo (8AM) + 1 drop QD (8PM) travoprost 0.004% or 0.0015%; 1 drop QD of placebo (8AM) + 1 drop QD (8PM) latanoprost 0.005%; or 1 drop BID of TIMOPTIC 0.5% (8AM and 8PM). 12 months.	787	64.2 years (22 – 94)	392 M 395 F
2 - C-97-72	Randomised, triple masked, multicentre, parallel group, active control in patients with open-angle glaucoma or ocular hypertension.	1 drop QD of placebo (8AM) + 1 drop QD (8PM) travoprost 0.004% or 0.0015%; or 1 drop of TIMOPTIC 0.5% (8AM and 8PM). 6 months.	594	63.7 years (21 – 91)	293 M 301 F
3 - C-97-73	Randomised, multicentre, triple-masked, vehicle-controlled, parallel group study in patients with open-angle glaucoma or ocular hypertension who were uncontrolled after a 3-week run-in on TIMOPTIC 0.5% dosed BID.	1 drop QD (8PM) of travoprost 0.004% or 0.0015% plus 1 drop BID of open-label TIMOPTIC 0.5% (8AM and 8PM); or 1 drop QD (8PM) of placebo plus 1 drop BID of open-label TIMOPTIC 0.5% (8AM and 8PM). 6 months.	410	63.7 years (11 – 89)	180 M 230 F
4 - C-97-79	Randomised, multicenter, triple-masked, active controlled, parallel group study in patients with open-angle glaucoma or ocular hypertension.	1 drop QD of placebo (9AM) + 1 drop QD (9PM) travoprost 0.004% or 0.0015%; or 1 drop BID of TIMOPTIC 0.5% (9AM and 9PM). 9 months.	572	63.3 years (31 – 88)	284 M 288 F
5 - C-01-74	Randomized, double-masked, multicenter, parallel group, active-controlled in patients with open-angle glaucoma or ocular hypertension.	1 drop QD of placebo (9AM) + 1 drop QD (9PM) travoprost 0.004%; or 1 drop QD of latanoprost/timolol 0.5% (9AM) + 1 drop QD of placebo (9PM). 6 weeks	106	68.0 years (34 – 86)	46 M 60 F

Mean baseline IOP and mean change from baseline IOP measurements.

Study (Duration)	Baseline mean IOP (mmHg)			Mean IOP change from baseline (mmHg)		
	8 AM	**10 AM**	**4 PM**	**8 AM**	**10 AM**	**4 PM**
C-97-71						
TRAVATAN	26.8	25.2	24.6	-7.6	-7.4	-6.9
Timolol	26.9	25.3	24.6	-6.7*	-6.1*	-5.3*
Latanoprost	26.9	25.2	24.9	-7.7	-6.9	-6.3*
C-97-72						
TRAVATAN	27.3	25.7	25.1	-7.6	-7.2	-7.0
Timolol	27.4	25.8	25.4	-6.8*	-6.0*	-5.1*
C-97-73						
TRAVATAN / timolol	26.0	24.5	24.6	-6.8	-6.4	-6.0
Timolol	26.4	24.8	24.4	-2.6*	-1.8*	-1.6*
C-97-79[a]						
TRAVATAN	27.4	26.5	25.6	-8.8	-8.7	-8.2
Timolol	27.0	26.2	25.1	-7.7*	-7.5*	-6.6*
C-01-74[b]						
TRAVATAN	25.3	--	24.3	-6.9	--	-6.8
latanoprost / timolol	24.6	--	23.9	-6.4	--	-6.1

[a] The C-97-79 IOP measurements were taken at 9AM, 11AM and 4PM.
[b] The C-01-74 IOP measurements were taken at 9AM and 5PM.
*P<0.05 for between group comparisons versus TRAVATAN.

A 9-month pivotal clinical study with a 5-year extension phase was conducted to evaluate the long-term safety of once-daily evening dosing of TRAVATAN® Solution. Overall, 196 patients were enrolled into the 5-year extension clinical trial, 67 of which were exposed to TRAVATAN® Solution, 0.004%. TRAVATAN® Solution maintained clinically relevant long-term IOP control in all patients for nearly 6 years. The overall incidence of iris discoloration in patients treated with TRAVATAN® Solution was 11.9%. The adverse events of iris discoloration were mild and did not interrupt patient continuation in the study. The observation of increased iris discoloration did not affect the incidence, nature or severity of adverse events recorded in the study. IOP reduction was similar regardless of the development of increased iris discoloration.

In a 3 month clinical study, TRAVATAN® Z solution dosed QD in the evening produced equivalent IOP lowering efficacy compared to TRAVATAN® solution QD. The maximum mean IOP reductions for TRAVATAN® Z solution (8.5 mmHg) and TRAVATAN® solution (8.4 mmHg) correspond to approximate 31% IOP reductions in each group. All mean reductions were clinically relevant and statistically significant ($p<0.0001$).

INDICATIONS AND USAGE

TRAVATAN® (travoprost) Ophthalmic Solution and TRAVATAN® Z (travoprost) Ophthalmic Solution are indicated for the reduction of intraocular pressure in patients with open-angle glaucoma or ocular hypertension

CONTRAINDICATIONS

Known hypersensitivity to any of the ingredients in these products (see Pharmaceutical Information). TRAVATAN® (Travoprost) ophthalmic Solution or TRAVATAN® Z (travoprost) Ophthalmic Solution may interfere with the maintenance of pregnancy and should not be used by women during pregnancy or by women attempting to become pregnant.

WARNINGS

Ocular Effects

TRAVATAN® (travoprost) Ophthalmic Solution or TRAVATAN® Z (travoprost) Ophthalmic Solution may gradually change eye color, increasing the amount of brown pigmentation in the iris by increasing the number of melanosomes (pigment granules) in melanocytes. The long term effects on the melanocytes and any consequences of potential injury to the melanocytes and/or deposition of pigment granules to other areas of the eye are currently unknown. 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 brownish. The change in iris color occurs slowly and may not be noticeable for months to years. In clinical trials, iris pigmentation was detected as early as 3 months. This change in eye color has predominantly been seen in patients with mixed colored irides, i.e., blue-brown, grey-brown, yellow-brown and green-brown; however, it has also been observed in patients with brown eyes. These changes may be permanent. Patients should be informed of the possibility of iris color change. There are no clinical data on treatment with TRAVATAN® solution beyond five years.

Periorbital and/or eyelid skin darkening has been reported in association with the use of TRAVATAN® and TRAVATAN® Z (travoprost) Ophthalmic Solution.

TRAVATAN® and TRAVATAN® Z (travoprost) Ophthalmic Solution may gradually change eyelashes in the treated eye; these changes include: increased length, thickness, pigmentation, and/or number of lashes. During long-term clinical trials, eyelash photographs taken periodically during the studies, revealed an overall incidence of eyelash changes of 61%. The overall incidence of patient complaints regarding these changes was 0.8%. Changes in eyelashes may be noticed as early as one and a half months after initiation of treatment. The mechanism of eyelash changes and their long term consequence are currently unknown.

Patients who receive treatment in only one eye may experience increased brown pigmentation of the iris, periorbital and/or eyelid tissue, and eyelashes in the treated eye. They may also experience disparity between the eyes in length, thickness, and/or number of eyelashes. These changes in pigmentation and lash growth may be permanent.

There is no experience of TRAVATAN® or TRAVATAN® Z (travoprost) Ophthalmic Solution in inflammatory ocular conditions; nor in neovascular or angle-closure glaucoma.

Systemic Effects

Use in Pregnancy: No adequate and well-controlled studies have been performed in pregnant women. Travoprost, like all FP agonists, may interfere with the maintenance of pregnancy and should not be used by women during pregnancy or by women attempting to become pregnant.

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 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.

PRECAUTIONS

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 epithelial surface (see Information for Patients).

Patients may slowly develop increased brown pigmentation of the iris. This change may not be noticeable for months to years (see Warnings).

TRAVATAN® and TRAVATAN® Z (travoprost) Ophthalmic Solution 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 $F_{2\alpha}$ analogues. 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. TRAVATAN® and TRAVATAN® Z Solution should be used with caution in these patients.

In phase III clinical trials, TRAVATAN® Solution was studied adjunctively with TIMOPTIC*. No additional adjunctive studies have been done.

TRAVATAN® Solution has been studied in patients with mild to severe hepatic impairment (Childs-Pugh Classification A - C) and also in patients with mild to severe renal impairment (creatinine clearance from as low as 14 mL/min/1.73 m^2 to 77 mL/min/1.73 m^2). No clinically relevant changes in hematology, blood chemistry, urinalysis laboratory data or plasma concentrations of free acid were observed in patients with impaired (mild, moderate, or severe) hepatic or renal function. No dosage adjustment is necessary in patients with hepatic or renal impairment.

Patients should remove contact lenses prior to administration of the solution. Lenses may be reinserted 15 minutes following administration of TRAVATAN® or TRAVATAN® Z Solution.

Since prostaglandins are biologically active and may be absorbed through the skin, women who are pregnant or attempting to become pregnant should exercise appropriate precautions to avoid direct exposure to the contents of the bottle. In case of accidental contact with the contents of the bottle, thoroughly cleanse the exposed area with soap and water immediately.

Use in Nursing Mothers:

A study in lactating rats demonstrated that radiolabeled travoprost and/or its metabolites were excreted in milk. It is not known whether this drug or its metabolites are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when TRAVATAN® or TRAVATAN® Z Solution is administered to a nursing woman.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Information for Patients

Patients should be advised concerning all the information contained in the Warnings and Precautions sections.

Patients should also be instructed to avoid allowing the tip of the dispensing container to contact the eye or surrounding structures because this could cause the tip to 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.

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

Patients should be advised that if they develop symptoms of hypersensitivity, particularly conjunctivitis and lid reactions, they should immediately seek their physician's advice.

Patients should also be advised that TRAVATAN® Solution contains benzalkonium chloride which may be absorbed by contact lenses. Contact lenses should be removed prior to administration of the solution. Lenses may be reinserted 15 minutes following administration of TRAVATAN® Solution. TRAVATAN® Z solution does not contain benzalkonium chloride; however, lenses should also be reinserted 15 minutes following administration.

If more than one topical ophthalmic drug is being used, the drugs should be administered at

least five (5) minutes apart.

ADVERSE REACTIONS

Ocular hyperemia was reported in 40% of all patients receiving TRAVATAN® (travoprost) Ophthalmic Solution and TRAVATAN® Z (travoprost) Ophthalmic Solution. Approximately 80 to 90% of the ocular hyperemia was mild in intensity and subsided over time without treatment. Up to three percent of the patients discontinued therapy due to conjunctival hyperemia. Table 1 summarizes adverse reactions reported with TRAVATAN® solution.

During clinical studies, there were extremely rare reports of the following: choroidal nevus, retinal detachment, retinal hemorrhage, retinal pigmentation, and vitreous detachment.

Table 1
Overall (Related & Unrelated) Frequency and Incidence of Adverse Events Occurring at an Incidence ≥ 1.0%

	TRAVATAN 0.004% N=656		TRAVATAN 0.004% + Timolol 0.5% N=145	
	N	**%**	**N**	**%**
Ocular				
Hyperemia Eye	259	39.5	52	35.9
Discomfort Eye	35	5.3	7	4.8
Pruritus Eye	48	7.3	5	3.4
Visual Acuity Decrease	29	4.4	6	4.1
Iris Discoloration[a]	15	2.3	0	
Dry Eye	20	3.0	8	5.5
Foreign Body Sensation	24	3.7	4	2.8
Pain Eye	33	5.0	6	4.1
Keratitis	17	2.6	3	2.1
Vision Blurred	13	2.0	3	2.1
Cataract NOS	13	2.0	1	0.7
Blepharitis	11	1.7	2	1.4
Cells	7	1.1	6	4.1
Hemorrhage Subconjunctival	7	1.1	0	
Conjunctivitis	10	1.5	2	1.4
Flare	7	1.1	2	1.4
Photophobia	8	1.2	4	2.8
Tearing	7	1.1	3	2.1
Lid Disorder	1[b]	0.2	3[c]	2.1
Eye Fatigue	2	0.3	2	1.4
Sticky Sensation	1	0.2	2	1.4
Nonocular				
Body as a Whole				
Surgical/Medical Proc	31	4.7	4	2.8
Infection	24	3.7	3	2.1
Headache	20	3.0	2	1.4
Pain	14	2.1	0	
Injury Accidental	17	2.6	1	0.7
Cold Syndrome	10	1.5	3	2.1
Flu Syndrome	17	2.6	2	1.4
Allergy	3	0.5	2	1.4
Cardiovasc System				
Hypertens	27	4.1	2	1.4
Digestive System				
GI Disorder	10	1.5	1	0.7
Metabolic and Nutritional				
Hypercholesteremia	11	1.7	0	
Nervous				
Depression	9	1.4	2	1.4
Respiratory System				
Sinusitis	11	1.7	3	2.1
Bronchitis	7	1.1	1	0.7
Rhinitis	7	1.1	1	0.7
Urogenital System				
Infection Urinary Tract	7	1.1	3	2.1
Prostate Disorder	6	0.9	2	1.4

[a] increase in brown pigmentation of the iris
[b] Lid pigment (1)
[c] prominent vessel (1), sore spot (1), lid lesion (1)

A similar safety profile was observed in a clinical trial of three months duration, comparing therapy with TRAVATAN® Z Solution (399 patients dosed QD in the evening) to TRAVATAN® Solution (400 patients dosed QD in the evening).

The following serious, unexpected reactions reported during the post-market use of TRAVATAN® Solution in clinical practice and in the literature have been included based on the frequency of reporting, possible causal connection to TRAVATAN® Solution, or a combination of these factors:

Ocular Disorders: Corneal edema and macular edema.
Nonocular Disorders:
Cardiac disorders: bradycardia and tachycardia.
General disorders and administration site conditions: chest discomfort.
Respiratory, thoracic and mediastinal disorders: asthma and dyspnea.

A few case 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.

SYMPTOMS & TREATMENT OF OVERDOSAGE

For management of suspected drug overdosage, including oral ingestion, contact your regional poison control centre.

A single-dose intravenous study in rats was conducted to elucidate maximal acute hazard. The dose employed was 250,000-times the proposed daily clinical exposure and over 5000-times the possible exposure from the entire contents of one product container. No treatment related pharmacotoxic signs were present in the animals receiving travoprost.

If overdosage with TRAVATAN® (travoprost) Ophthalmic Solution or TRAVATAN® Z (travoprost) Ophthalmic Solution occurs, treatment should be symptomatic.

DOSAGE AND ADMINISTRATION

The recommended dosage is one drop in the affected eye(s) once-daily. Optimal effect is observed with evening dosing. The dosage of TRAVATAN® (travoprost) Ophthalmic Solution or TRAVATAN® Z (travoprost) Ophthalmic Solution should not exceed once-daily since it has been shown that more frequent administration may decrease the intraocular pressure lowering effect.

Reduction of intraocular pressure starts approximately 2 hours after administration and the maximum effect is reached after 12 hours.

TRAVATAN® or TRAVATAN® Z Solution may be used concomitantly with topical ophthalmic beta-blockers to lower intraocular pressure. If more than one topical ophthalmic drug is being used, the drugs should be administered at least five (5) minutes apart.

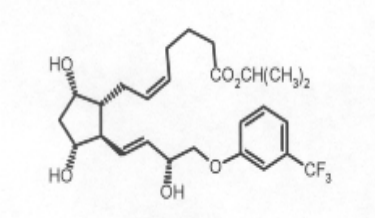
PHARMACEUTICAL INFORMATION

Drug Substance:

Common Name: Travoprost

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

Structural Formula:



Molecular Formula: $C_{26}H_{35}F_3O_6$.

Molecular Weight: 500.56

Description: Travoprost is a clear, colorless to pale yellow oil

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

Composition:

TRAVATAN® (travoprost) Ophthalmic Solution 0.004% is supplied as a sterile, buffered aqueous solution of travoprost with a pH of approximately 6.0 and an osmolality of approximately 290 mOsmol/kg.

Each mL of TRAVATAN® Solution 0.004% contains 40 μg travoprost. Preservative: benzalkonium chloride 0.015%. Inactive Ingredients: polyoxyl 40 hydrogenated castor oil, tromethamine, boric acid, mannitol, edetate disodium, sodium hydroxide and/or hydrochloric acid (to adjust pH) and purified water.

TRAVATAN® Z (travoprost) Ophthalmic Solution is supplied as a sterile, buffered aqueous solution of travoprost with a pH of approximately 5.7 and an osmolality of approximately 290 mOsmol/kg.

Each mL of TRAVATAN® Z Solution 0.004% contains 40 μg travoprost. Inactive Ingredients: polyoxyl 40 hydrogenated castor oil, purified water, *sof*Zia® preservative system (boric acid, propylene glycol, sorbitol, zinc chloride), and sodium hydroxide and/or hydrochloric acid (to adjust pH). Preserved in the bottle with an ionic buffered system, *sof*Zia®.

Stability and Storage Recommendations: Store between 2° to 25°C.

AVAILABILITY OF DOSAGE FORMS

Pr TRAVATAN® (travoprost) Ophthalmic Solution and TRAVATAN® Z (travoprost) Ophthalmic Solution are sterile, isotonic, buffered, preserved, aqueous solutions supplied in the Alcon oval DROP-TAINER® dispenser bottle. This plastic oval-shaped dispenser bottle, containing 2.5mL or 5mL, includes a tamper-evident neck-band which shrinks to conform around the closure and neck area of the package.

INFORMATION FOR THE CONSUMER

Pr TRAVATAN® (travoprost) Ophthalmic Solution
Travoprost

Medicine to treat Elevated Intraocular Pressure

Information for the Patient: TRAVATAN® (travoprost) Ophthalmic Solution.

Read all of this leaflet carefully before you start using this medicine.

Keep this leaflet. You may need to read it again. If you still have questions after reading it, please ask your doctor or your pharmacist.

The active substance is travoprost 0.040 mg/mL.

Other ingredients: Benzalkonium chloride (preservative), polyoxyl 40 hydrogenated castor oil, tromethamine, edetate disodium, boric acid, mannitol, and purified water. Tiny amounts of hydrochloric acid or sodium hydroxide are added to maintain proper pH balance.

1. WHAT TRAVATAN® SOLUTION DOES

TRAVATAN® (travoprost) Ophthalmic Solution 0.004% is used to treat high pressure in the eye. This pressure can lead to an illness called **glaucoma**.

High pressure in the eye. Your eyeballs contain a clear, watery liquid which feeds the inside of the eye. Liquid is always emptying out of the eye, and more liquid is always being produced. If the eye fills up faster than it empties, the pressure inside the eye builds up. If it gets too high, it can damage your sight.

TRAVATAN® (travoprost) Ophthalmic Solution 0.004% is one of a group of medicines for glaucoma which contain prostaglandin analogues. It works by increasing the outflow of liquid,

which lowers the pressure in the eye. It may be used on its own or with other glaucoma eye drops, which also reduce pressure.

TRAVATAN® (travoprost) Ophthalmic Solution 0.004% is a liquid (a colourless to light yellow solution) supplied in a 2.5mL or 5mL plastic bottle with a screw cap.

2. BEFORE YOU USE TRAVATAN® SOLUTION

Do not use TRAVATAN® (travoprost) Ophthalmic Solution 0.004%...

- **If you are allergic** to travoprost, prostaglandin analogues or any of the other ingredients of TRAVATAN® Solution (see Other Ingredients).
- **If you are pregnant, or trying to become pregnant**
  Ask your doctor for advice.

Take special care using TRAVATAN® (travoprost) Ophthalmic Solution 0.004%...

- **If you wear soft contact lenses.** Don't use the drops with your lenses already in place. Wait 15 minutes after using the drops before putting your lenses back in. Benzalkonium chloride, a preservative in **TRAVATAN®** Solution, can discolour soft lenses.

- **if you are breast-feeding**, **TRAVATAN®** Solution may get into your breast milk. Ask your doctor for advice.

- **TRAVATAN®** Solution is not to be used by people under 18 years of age.

- **TRAVATAN® (travoprost) Ophthalmic Solution 0.004%** may increase the length, thickness, colour and/or number of your eyelashes.

- **TRAVATAN®** Solution may change the colour of your eye. It may make your iris (the coloured part of your eye) more brown.

- If you use **TRAVATAN® (travoprost) Ophthalmic Solution 0.004%** in one eye only, the possible change in colour in your iris, the skin around the eye or the change in the eyelashes may **appear in the treated eye only**.

- These changes in pigmentation and lash growth may be permanent.

- If the product comes into contact with the skin then it should be washed off straight away.

- Tell your doctor if you will be having eye surgery.

- Tell your doctor immediately if you develop an eye infection, irritation or suffer any damage to your eye while taking TRAVATAN® Solution.

Driving or using machines
You may find that your vision is blurred for a short time just after you use **TRAVATAN®** Solution. Do not drive or use machines until your vision is clear.

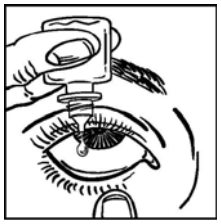
Please tell your doctor or pharmacist if you are taking (or recently took) any other medicines. Also mention those medicines that you bought without prescription.

3. HOW TO USE TRAVATAN® SOLUTION

The usual dose

Adults: **1 drop in the eye or eyes, once a day.** Evening is the best time to take your medication.
Only use **TRAVATAN®** Solution in both eyes if your doctor told you to. Take it for as long as your doctor told you to.

Only use **TRAVATAN®** Solution in your eyes.



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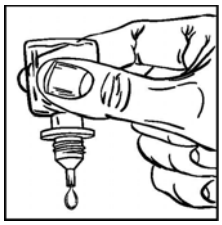


2

How much to use
- Get the **TRAVATAN®** Solution bottle and a mirror (if needed)
- Wash your hands
- Twist off the cap
- 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 here (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 dropper. It could get germs on the dropper tip.
- Gently squeeze the bottle to release one drop of **TRAVATAN®** Solution at a time (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 a drop misses your eye, wipe it off with a tissue and try again.

If you forget to use TRAVATAN® Solution, take your next scheduled dose. Do not use a double dose to make up.

If you are using other eye drops, wait at least 5 minutes between putting in **TRAVATAN®** Solution and the other drops.

Overdosage:
If you accidentally use too many drops, just go back to your regular once a day dosing the next day. If you have any concerns, talk to your doctor or pharmacist.

If you accidentally swallow this product, contact your doctor, regional poison control centre or hospital emergency department.

4. POSSIBLE SIDE EFFECTS

Some people who use TRAVATAN® (travoprost) Ophthalmic Solution 0.004% may have side effects. They can be unpleasant, but most of them soon pass.

You can usually carry on taking the drops, unless the effects are serious. If you're worried, talk to your doctor or pharmacist.

Common side effects

The following may affect approximately 1 in every 3 people.
Redness of the eye. Approximately 80 to 90% of the redness reported in clinical trials was mild and lessened over time without treatment.

One or more of these may affect approximately 5 in every 100 people.
Effects in the eye: burning or stinging upon instillation, itchy eye, change of colour of the iris, dry eye, foreign body sensation, eye or eyelid inflammation, pain in the eye, blurred vision, decreased vision, sensitivity to light.

Effects in the body: headache.

If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

5. STORING TRAVATAN® SOLUTION

Keep the drops in a safe place where children can't see or reach them.

This medicine has been prescribed for you personally. You must not pass it on to other people. It may harm them even if they have the same illness as you.

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

Don't use the drops after the expiry date (marked 'Exp') on the bottle and the box.

If you have any other questions about your medicines you should ask a doctor or pharmacist.

6. MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at: http://www.alcon.ca or by contacting the sponsor, ALCON Canada, at: 1-800-613-2245.

This leaflet was prepared by ALCON Canada Inc.

INFORMATION FOR THE CONSUMER

Pr TRAVATAN® Z (travoprost) Ophthalmic Solution, 0.004% w/v

Medicine to treat Elevated Intraocular Pressure

Information for the Patient: TRAVATAN® Z (travoprost) Ophthalmic Solution.

Read all of this leaflet carefully before you start using this medicine.

Keep this leaflet. You may need to read it again. If you still have questions after reading it, please ask your doctor or your pharmacist.

The active substance is travoprost 0.040 mg/mL.

Other ingredients: Preservative: *sof*Zia® (boric acid, propylene glycol, sorbitol, zinc chloride), polyoxyl 40 hydrogenated castor oil, and purified water. Tiny amounts of hydrochloric acid or sodium hydroxide are added to maintain proper pH balance.

1. WHAT TRAVATAN® Z OPHTHALMIC SOLUTION DOES

TRAVATAN® Z Solution is used to treat high pressure in the eye. This pressure can lead to an illness called **glaucoma**.

High pressure in the eye. Your eyeballs contain a clear, watery liquid which feeds the inside of the eye. Liquid is always emptying out of the eye, and more liquid is always being produced. If the eye fills up faster than it empties, the pressure inside the eye builds up. If it gets too high, it can damage your sight.

TRAVATAN® Z Solution is one of a group of medicines for glaucoma which contain prostaglandin analogues. It works by increasing the outflow of liquid, which lowers the pressure in the eye. It may be used on its own or with other glaucoma eye drops, which also reduce pressure.

TRAVATAN® Z Solution is a liquid (a colourless to light yellow solution) supplied in a 2.5mL or 5mL plastic bottle with a screw cap.

2. BEFORE YOU USE TRAVATAN® Z OPHTHALMIC SOLUTION

Do not use TRAVATAN® Z Solution...

- **If you are allergic** to prostaglandin analogues or any of the other ingredients (see Other Ingredients).
- **If you are pregnant, or trying to become pregnant**
  Ask your doctor for advice.

Take special care using TRAVATAN® Z Solution...

- **If you wear soft contact lenses.** Don't use the drops with your lenses already in place. Wait 15 minutes after using the drops before putting your lenses back in.

- **if you are breast-feeding**, **TRAVATAN® Z** Solution may get into your breast milk. Ask

your doctor for advice.

- **TRAVATAN® Z** Solution is not to be used by people under 18 years of age.

- **TRAVATAN® Z** Solution may increase the length, thickness, colour and/or number of your eyelashes.

- **TRAVATAN® Z** Solution may change the colour of your eye. It may make your iris (the coloured part of your eye) more brown.

- If you use **TRAVATAN® Z** Solution in one eye only, the possible change in colour in your iris, the skin around the eye or the change in the eyelashes may **appear in the treated eye only**.

- These changes in pigmentation and lash growth may be permanent.

- If the product comes into contact with the skin then it should be washed off straight away.

- Tell your doctor if you will be having eye surgery.

- Tell your doctor immediately if you develop an eye infection, irritation or suffer any damage to your eye while taking TRAVATAN® Z Solution.

Driving or using machines
You may find that your vision is blurred for a short time just after you use **TRAVATAN® Z** Solution. Do not drive or use machines until your vision is clear.

Please tell your doctor or pharmacist if you are taking (or recently took) any other medicines. Also mention those medicines that you bought without prescription.

3. HOW TO USE TRAVATAN® Z OPHTHALMIC SOLUTION

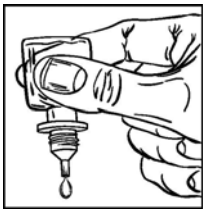
The usual dose

Adults: **1 drop in the eye or eyes, once a day.** Evening is the best time to take your medication.

Only use **TRAVATAN® Z** Solution in both eyes if your doctor told you to. Take it for as long as your doctor told you to.

Only use **TRAVATAN® Z** Solution in your eyes.

1



2

How to use

- Get the **TRAVATAN® Z** Solution bottle and a mirror (if needed).
- Wash your hands.
- Twist off the cap.
- 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 here (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 dropper. It could get germs on the dropper tip.
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This leaflet was prepared by ALCON Canada Inc.

PHARMACOLOGY

Travoprost is a $PGF_{2\alpha}$ analogue. It is the (+) isomer of fluprostenol isopropyl ester and the prodrug of the active free acid constituent.

In Vitro Studies

Receptor Binding

Receptor binding affinity was compared for the acid forms of travoprost and latanoprost. The two acid prostaglandin analogues had a high affinity binding for the FP-receptors (bovine corpus luteum membranes). Receptor interaction appeared to be at a single binding site. There was a low affinity for the other prostaglandin receptors. The parent free acid of travoprost is over 60-fold less potent in binding to other receptors. Travoprost demonstrates higher potency and higher selectivity for the FP receptor compared to latanoprost.

	Receptor affinity data for Travoprost and Latanoprost free acids (Ki, nM)					
	DP receptors	EP3 receptors	EP4 receptors	FP receptors	IP receptors	TP receptors
Travoprost free acid	46000	3500	12000	52	90000	120000
Latanoprost free acid	26000	7900	9000	92	> 90000	61000

Prostaglandin Functional Assays

Travoprost free acid was a potent and fully efficacious agonist in stimulating phosphoinositide (PI) turnover in Swiss 3T3 cells expressing a FP receptor. In contrast, latanoprost acid had lower potency than the travoprost free acid and was a partial agonist in this system.

	Second Messenger Study: Potency & Efficacy		
	FP PI turnover	DP cyclase stim	EP2 cyclase stim
Travoprost free acid	4 nM (Emax = 100%)	Inactive	Inactive
Latanoprost free acid	27 nM (Emax = 75%)	Inactive	Inactive

Travoprost acid did not demonstrate affinity for a panel of over 32 different non-prostanoid receptors including muscarinic, alpha-adrenergic, beta-adrenergic, and endothelin receptors at concentrations up to 10 uM.

Animal Pharmacology

In the cynomolgus monkey, instillation of a single dose of travoprost reduced IOP in a dose-related fashion, with a peak reduction of 30% with a 0.3 μg dose. Once daily dosing provided IOP reductions for a 24 hour period.

Reduction of IOP following b.i.d. Travoprost (AL-6221) in Lasered Cynomolgus Monkeys

Dose (ug)	Baseline IOP	Dose number/hour after dose Percent ± SEM (mmHg ± SEM)						
[Vehicle[1]]	(mmHg)	1/2[2]	1/4	1/6	4/16	5/2	5/4	5/6
0.1 [P/ P]	36.8	1.8 ± 6.4 (1.7 ± 2.6)	7.7 ± 6.8 (3.9 ± 3.0)	9.3 ± 8.1 (4.8 ± 3.8)	16.9 [4] ± 4.3 (6.8 ± 1.9)	22.7[4] ± 5.8 (9.3 ± 3.1)	21.8[4] ± 6.8 (9.2 ± 3.5)	15.3 ± 7.6 (6.6 ± 3.6)
Vehicle	41.4	16.4 ± 8.3 (8.4 ± 5.1)	19.0 ± 8.4 (10.2 ± 2.6)	20.7 ± 7.7 (10.6 ± 3.0)	8.1 ± 1.9 (3.8 ± 6.1)	14.7 ± 9.8 (8.4 ± 3.3)	16.9 ± 8.7 (9.0 ± 3.4)	9.4 ± 9.0 (6.4 ± 3.0)
0.3 [T.N.]	41.6	19.0[3] ± 4.1 (8.5 ± 1.9)	15.0[3] ± 2.5 (6.6 ± 1.3)	18.5[3] ± 3.0 (8.2 ± 1.5)	18.4 [3]± 5.9 (8.4 ± 2.8)	31.2[3] ± 3.7 (13.5 ± 2.1)	30.3[3] ± 3.8 (13.2 ± 2.0)	26.6[3] ± 3.6 (11.6 ± 1.9)
Vehicle	40.6	6.5 ± 4.7 (3.2 ± 2.5)	9.2 ± 5.7 (4.0 ± 3.7)	1.9 ± 4.5 (9.0 ± 3.8)	6.6[4] ± 2.6 (2.6 ± 4.3)	13.3[4] ± 4.8 (5.4 ± 4.0)	16.4 ± 4.3 (7.2 ±2.0)	14.6 ± 7.2 (7.0 ±1.6)
0.3 [P/ P]	36.8	19.5[4] ± 3.7 (7.7 ± 2.1)	25.7[4] ± 5.0 (10.8 ± 3.4)	22.1[4] ± 5.9 (9.2 ± 3.4)	29.9[4] ± 3.7 (11.9 ± 2.4)	28.6[4] ± 5.2 (11.9 ± 3.2)	28.1[4] ± 5.7 (11.9 ± 3.4)	20.7[4] ± 5.3 (9.0 ± 3.1)
Vehicle	34.7	7.2 ± 4.8 (3.0 ± 4.3)	6.1 ± 7.0 (3.5 ± 2.9)	5.1 ± 8.1 (3.5 ± 2.4)	2.6 ± 5.6 (1.5 ± 4.5)	1.1 ± 6.0 (1.4 ± 3.9)	4.6 ± 7.5 (2.7 ± 3.7)	+6.8 ± 6.7 (+2.7 ± 4.2)

1 P/P = phosphate buffered saline with polysorbate 80; T.N. = Tears Naturale

2 b.i.d. dosing at 0900 and 1700 hours; Dose number/hour after dose

3 $p<0.01$

4 $p<0.05$

In one cross-over study, the optic nerve head blood flow (ONHBF) was significantly increased 13.4% (± 3.9%) in 15 Dutch-belted rabbits following once-daily topical ocular dosing with travoprost 0.004% for one week. Systemic circulatory parameters were not affected by drug treatment.

Clinical Efficacy

TRAVATAN® (travoprost) Ophthalmic Solution 0.004% dosed once-daily in patients with open-angle glaucoma or ocular hypertension, having a baseline mean IOP between 25 to 27 mmHg, produced significant reductions in intraocular pressure (IOP) when used either as a single therapy or adjunctively to TIMOPTIC* (timolol maleate ophthalmic solution) 0.5% BID.

TRAVATAN® Solution, dosed QD in the evening, reduced IOP 6.7 to 9.0 mmHg. Stable 24-hour IOP reductions were achieved as early as 2 weeks after initiation of therapy and were maintained over the 6 to 12 month treatment period in three (3) well-controlled studies. The IOP reductions with TRAVATAN® Solution were superior to those obtained with TIMOPTIC* and equal or better than those obtained with XALATAN* (latanoprost ophthalmic solution) 0.005% QD. TRAVATAN® Solution 0.004% demonstrated an earlier stabilization of IOP reduction and better overall IOP control over 24 hours compared to XALATAN* 0.005%. TRAVATAN® Solution 0.004% was significantly more effective (up to 1.4 mmHg) than XALATAN* 0.005% in reducing IOP in black patients

A responder analysis (IOP reduction $\geq$ 30% or mean IOP $\leq$ 17 mmHg), based on the data from the three pivotal studies, demonstrated that TRAVATAN® Solution 0.004% had a significantly higher responder rate (56%) compared to XALATAN* 0.005% (50%) which were both significantly greater than TIMOPTIC* (40%).

Responder Analyses Based on Percent IOP Reduction ($\geq$30%) or Mean IOP ($\leq$17 mmHg)*

Study Duration	Treatment Group		
	TRAVATAN 0.004%	TIMOPTIC 0.5%	XALATAN 0.005%
Study C-97-71 12 months	54.7 [1, 2]	39	49.6[3]
Study C-97-72 6 months	50.5[1]	35.4	Not applicable
Study C-97-79 9 months	63.3[1]	47.1	Not applicable

*Response to therapy was based on IOP reduction ≥ 30% from the corresponding diurnal baseline or a mean IOP ≤ 17 mmHg. The data is combined over visit and time of day and represents the percentage of patients that responded to therapy as defined above. Results are based upon the per protocol data sets.

[1] p<0.0001 comparing Travoprost 0.004% vs. Timoptic.
[2] p≤0.0163 comparing Travoprost 0.004% vs. Xalatan.
[3] p≤0.0106 comparing Xalatan vs. Timoptic.

In a 6-month well-controlled study, patients with a mean IOP of 24-26 mmHg on TIMOPTIC 0.5% ~~b.i.d.~~ BID who were treated with TRAVATAN® Solution 0.004% dosed QD adjunctively to TIMOPTIC* demonstrated an additional 6-7 mmHg reduction in IOP.

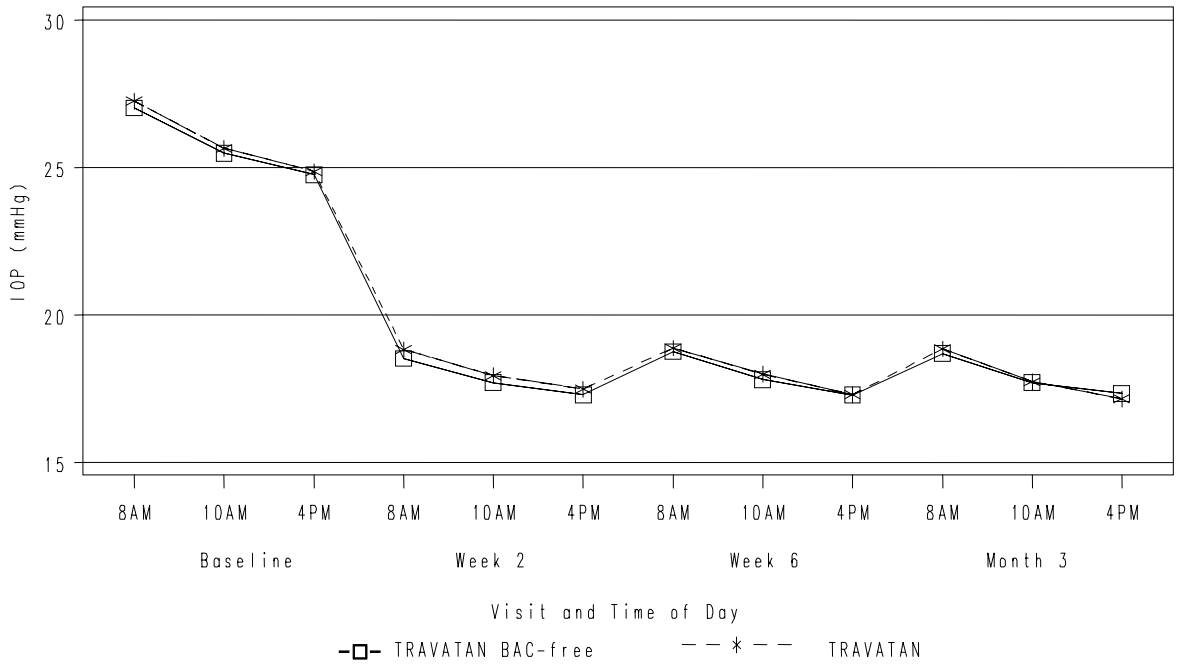
In a clinical pharmacology study patients were dosed one drop (TRAVATAN® solution or TRAVATAN® Z solution) in each study eye at 8PM for two weeks. TRAVATAN® Z solution and TRAVATAN® solution produced statistically significant and clinically relevant mean IOP reductions from baseline for up to 60 hours following the final dose of study drug. Mean IOP reductions, across the 5 post-dosing time points ranged from 4.9 to 8.2 mmHg for TRAVATAN® Z solution and from 5.2 to 8.6 mmHg for TRAVATAN® solution. In addition, no safety issues were identified in a population of adult and elderly patients with open-angle glaucoma or ocular hypertension.

A benzalkonium chloride free formulation of TRAVATAN® solution provides patients with open angle glaucoma or ocular hypertension with the additional potential benefit of decreasing their exposure to benzalkonium chloride and provides an alternative IOP-lowering treatment for patients intolerant to benzalkonium chloride.

In a 3 month clinical study, TRAVATAN® Z solution dosed QD in the evening produced statistically equivalent IOP lowering efficacy compared to TRAVATAN® solution QD. Mean IOP reductions from baseline for TRAVATAN® Z and TRAVATAN® solution were clinically relevant and statistically significant at all measurement times. Mean IOP reductions in the per protocol and intent-to-treat analyses ranged from 7.3 to 8.5 mmHg for TRAVATAN® Z solution and from 7.4 to 8.4 mmHg for TRAVATAN® solution (Figure 1). The maximum mean IOP reductions for TRAVATAN® Z solution (8.5 mmHg) and TRAVATAN® solution (8.4 mmHg) correspond to approximate 31% IOP reductions in each group.

TRAVATAN® Z and TRAVATAN® solution provide similar IOP control, with up to 54% of patients in the TRAVATAN® Z solution group and up to 58% of patients in the TRAVATAN® solution group achieving clinically relevant IOP response (IOP<18 mmHg). IOP response to treatment between groups was similar and not statistically significantly different at each study visit and time (p≥0.2198 across both analyses).

Figure 1: Mean IOP (mmHg) for TRAVATAN® Z and TRAVATAN®



TRAVATAN® BAC-free = TRAVATAN® Z

TOXICOLOGY

Acute Toxicity

Travoprost was demonstrated to have a low order of acute toxicity. 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). No significant systemic effects were observed.

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

Subchronic, Chronic Toxicity

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.

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 μg/kg/day.

Chronic systemic administration (subcutaneous) 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.

Carcinogenesis

Two year bioassays, in which rats and mice were dosed with travoprost by subcutaneous injection at doses up to 100 micrograms/kg/day (2,500 times the clinical dose), revealed no evidence of carcinogenic effect.

Mutagenesis

Travoprost was not mutagenic in bacteria, in one mouse lymphoma assay, in the mouse micronucleus tests nor in the rat chromosome aberration assay. In another mouse lymphoma

assay, higher concentrations of travoprost were slightly mutagenic only in the presence of activation enzymes.

Reproduction & Teratology

Travoprost did not affect mating or fertility indices in male or female rats and mice at subcutaneous doses up to 10 μg/kg/day (250 times the recommended human dose). The mean number of corpora lutea was slightly reduced and an increase in post-implantation loss was detected at that dose, but was not affected at 3 μg/kg/day (75 times the maximum recommended human dose).

In teratology studies conducted in pregnant rats and mice, travoprost reduced fetal viability when administered daily during the period of major organogenesis at doses as low as 1.0 (mice) and 10 (rats) μg/kg/day (25 and 250 times the maximum recommended human dose, respectively) with the lowest no effect level at 0.3 μg/kg/day (7.5 times the maximum recommended human dose). The incidence of skeletal malformations was slightly increased in fetuses of rat dams receiving travoprost by subcutaneous injection at 10 μg/kg/day (250 times the maximum recommended human dose), but not at 3 μg/kg/day (75 times the maximum recommended human dose). No fetal abnormalities were observed in mice at 1.0 μg/kg/day (25 times the maximum recommended human dose).

Pregnant rats dosed subcutaneously with up to 0.72 μg/kg/day from gestation Day 6 through lactation day 20 showed gestation length reduced in a dose related manner and the number of stillborn pups was increased. Surviving pup body weights were reduced. Pup development was affected as demonstrated by delayed static-righting reflex, eye opening and pinna detachment, delayed preputial separation and decrease in motor activity parameters. The no-observed adverse effect level was 0.1 μg/kg/day (2.5 times the human recommended dose).

BIBLIOGRAPHY

1. Goldberg I, Cunha-Vaz J, Jakobsen J-E, Nordmann JP, Trost E, Sullivan EK, The International Travoprost Study Group. Comparison of Topical Travoprost eye drops given once daily and timolol 0.5% given twice daily in patients with open-angle glaucoma or ocular hypertension. J Glaucoma 2001; 10: 414-422

2. Gross R, Peace JH, Smith SE, Walters TR, DuBiner HB, Weiss MJ, Ochsner KI, Duration of IOP reduction with travoprost BAK-free solution. J Glaucoma 2008; 17(3): 217-222.

3. Lewis RA et al. Travoprost 0.004% With and Without Benzalkonium Chloride: A Comparison of Safety and Efficacy. J Glaucoma 2007; 16(1): 98-103.

4. Netland PA, Landry T, Sullivan EK, Andrew R, Silver L, Weiner A, Mallick S, Dickerson J, Bergamini MVW, Robertson SM, Davis AA. The Travoprost Study Group. Travoprost compared with latanoprost and timolol in Patients with open-angle glaucoma or ocular hypertension. Am J Ophthalmol 2001; 132: 472-484.

5. Orengo-Nania S, Landry T, von Tress M, Silver L, Weiner A, Davis AA, The Travoprost Study Group. Evaluation of Travoprost as adjunctive therapy in patients with uncontrolled intraocular pressure while using timolol 0.5%. Am J Ophthalmol 2001; 132: 860-868.

6. Sharif NA, Davis TL, Williams GW. [^{3}H]AL-5848 ([^{3}H] 9β -(+)-Fluprostenol). Carboxylic acid of Travoprost (AL-6221), a novel FP prostaglandin to study the pharmacology and autoradiographic localization of the FP receptor. J Pharm Pharmacol 1999; 51: 685-694.

7. Sorbera L, Castaner J (2000). Travoprost. Drugs Future 25 (1): 41-45.

8. Konstas AGP, Mikropoulos D, Kaltsos K, Jenkins JN, Stewart WC. 24-hour intraocular pressure control obtained with evening versus morning dosed travoprost in primary open-angle glaucoma. Ophthalmology 2006; 113(3): 446-450.

10. Fellman RL, Sullivan EK, Ratliff M, Silver LH, Whitson JT, Turner FD, Weiner AL, Davis AA, The Travoprost Study Group. Comparison of Travoprost 0.0015% and 0.004% with Timolol 0.5% in Patients with Elevated Intraocular Pressure – A 6-month, Masked, Multicenter trial. Ophthalmology 2002; 109(5) 998–1008.

11. The AGIS Investigators. The Advanced Glaucoma Intervention Study (AGIS): 7. The relationship between control of intraocular pressure and visual field deterioration. Am J Ophthalmol 2000;130(4):429-40.

*TIMOPTIC is a registered trademark of Merck & Co. Inc.
*XALATAN is a registered trademark of Pharmacia Corp.

U.S. Patent Nos. 5,631,287; 5,849,792; 5,889,052; 6,011,062 and 6,235,781