

# TRAVATAN<sup>®</sup>

*Travoprost Eye Drops 0.004%*

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## Presentation

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TRAVATAN Eye Drops have been formulated as a sterile, preserved solution for topical application to the eye.

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## Uses

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### **Actions**

Travoprost is an ester prodrug of a PGF<sub>2α</sub> analogue and is hydrolysed to the active acid. The free acid is a prostaglandin FP receptor agonist. PGF<sub>2α</sub> analogues are believed to reduce the intraocular pressure (IOP) by increasing uveoscleral outflow. The exact mechanism of action is yet unknown.

Reduction of the IOP in man starts about two hours after administration and maximum effect is reached after twelve hours. Pressure reduction is maintained for at least twenty-four hours. Glaucoma is defined as an optic neuropathy resulting in optic nerve head damage and visual field loss. The pathogenesis of glaucoma is multi-factorial; the primary risk factors, however, are considered to be sustained elevated IOP and poor ocular perfusion. Pivotal clinical studies have demonstrated that TRAVATAN Eye Drops are effective as monotherapy at reducing intraocular pressure. In addition, travoprost slightly, but significantly, increased optic nerve head blood flow in a single study in rabbits.

### **Pharmacokinetics**

Travoprost is absorbed into the eye following topical ocular administration where it is hydrolysed to the active free acid. Following administration of 1.2mcg <sup>3</sup>H-travoprost in rabbits, the highest concentrations of radioactivity are found in the cornea, conjunctiva, aqueous humour and iris ciliary body. Maximum levels were observed 0.5-2 hours after instillation. Radioactivity concentrations in most ocular tissues declined with half-lives of less than 2 hours (>10 hours in cornea and lens). Systemic exposure is low. Maximum plasma concentrations of 0.08 ng equivalent/g were observed at 0.5 hours and declined rapidly thereafter.

The metabolic pathways of the acid parallel those of endogenous PGF<sub>2α</sub> and are characterised by reduction of the 13-14 double bond, oxidation of the 15-hydroxyl and β-oxidative cleavage of the carboxylic acid chain.

Following topical ocular administration of TRAVATAN Eye Drops to healthy volunteers, low systemic exposure to active free acid was demonstrated. Peak active free acid plasma concentrations of 25 pg/mL or less were observed between 10 and 30 minutes post-dose. Thereafter, plasma levels declined rapidly to below the 10 pg/mL assay quantitation limit before 1 hour post-dose. Due to the low plasma concentrations and rapid elimination following topical dosing, the elimination half-life of active free acid in man could not be determined.

### **Indications**

TRAVATAN Eye Drops are indicated to decrease elevated intraocular pressure in:

- ocular hypertension
  - open-angle glaucoma
- as monotherapy or as adjunctive therapy.

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## Dosage and Administration

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Instil one drop of TRAVATAN Eye Drops in the conjunctival sac of the affected eye(s) each day. Optimal effect is obtained if the dose is administered in the evening.

If more than one topical ophthalmic medicinal product is being used, the medicines must be administered at least 5 minutes apart.

When substituting another ophthalmic antiglaucoma agent with TRAVATAN Eye Drops, discontinue the other agent and start the following day with TRAVATAN Eye Drops.

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## Contraindications

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TRAVATAN Eye Drops are contraindicated in patients with a known hypersensitivity to travoprost or any of the excipients (see List of Excipients).

TRAVATAN Eye Drops are also contraindicated in pregnant women or women attempting to become pregnant (see Use in Pregnancy).

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## Warnings and Precautions

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### ***Not for injection or oral ingestion***

TRAVATAN Eye Drops have not been studied in patients with narrow-angle glaucoma.

TRAVATAN Eye Drops may gradually change the eye colour by increasing the number of melanosomes (pigment granules) in melanocytes. Before treatment is instituted patients must be informed of the possibility of these changes. Unilateral treatment can result in permanent heterochromia. The long term effects on the melanocytes and any consequences thereof are currently unknown. The change in iris colour occurs slowly and may not be noticeable for months to years. It may be permanent. The change in eye colour has predominantly been seen 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. 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. After discontinuation of therapy, no further increase in brown iris pigment has been observed.

Periorbital and/or eyelid skin darkening has been reported in association with the use of TRAVATAN Eye Drops.

TRAVATAN Eye Drops may gradually change eyelashes in the treated eye(s); these changes include: increased length, thickness, pigmentation, and/or number of lashes.

There is no experience of TRAVATAN Eye Drops in inflammatory ocular conditions, inflammatory, neovascular, angle-closure or congenital glaucoma and only limited experience in open-angle glaucoma of pseudophakic patients and in pigmentary glaucoma.

Although not reported during pivotal clinical trials with TRAVATAN Eye Drops, macular oedema, including cystoid macular oedema, has been reported during treatment with prostaglandin F<sub>2α</sub> 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 oedema.

Benzalkonium chloride, which is commonly used as a preservative in ophthalmic products, has been reported to cause punctate keratopathy and/or toxic ulcerative keratopathy. Since TRAVATAN

contains benzalkonium chloride, close monitoring is required with frequent or prolonged use in dry eye patients, or in conditions where the cornea is compromised.

### ***Use in Pregnancy***

#### **CATEGORY B3**

Travoprost and/or its metabolites crossed the placenta in rats. Travoprost was teratogenic in rats at IV doses of 10mcg/kg/day, equivalent to 98 times the expected human exposure at the proposed dose; it increased the incidence of hydrocephaly and bone abnormalities (eg. Vertebral malformations). Travoprost was not teratogenic in rats at IV doses of up to 3mcg/kg/day (29 times the expected human exposure) or in mice at SC doses of up to 0.3mcg/kg/day (1.2 times the human exposure). When administered during organogenesis (gestation days 6 to 17), travoprost produced increases in postimplantation loss and early delivery in mice at SC doses of 1mcg/kg/day (4 times the human exposure) and in rats at IV doses of 10mcg/kg/day (54 times the expected human exposure) administered from 2 weeks prior to mating to gestation day 7.

Travoprost Eye Drops. 0.003% administered to rabbits during organogenesis, appeared to increase incidence of fetal loss.

In rats administered travoprost from gestation day 7 to lactation day 21 by SC injection, abortions occurred at 0.72mcg/kg/day (4 times the expected human exposure), and decreased gestation length and increased stillbirths (see also Use in Lactation) occurred at  $\geq 0.12$ mcg/kg/day (0.65 times the expected clinical exposure).

No adequate and well-controlled studies have been performed in pregnant women. Travoprost may interfere with the maintenance of pregnancy. It should not be used by women during pregnancy or by women attempting to become pregnant.

### ***Use in Lactation***

An animal study showed that travoprost and/or its metabolites were excreted in rat milk. Increased pup mortality and depressed pup growth and development occurred in rats subcutaneously administered travoprost to dams from gestation day 7 to lactation day 21 at  $\geq 0.12$ mcg/kg/day, corresponding to exposures 0.65 times the expected human exposure. There are no data on the excretion of travoprost into human milk or on the safety of travoprost exposure in infants. Because many drugs are excreted in human milk, nursing women who use Travatan should stop breastfeeding.

### ***Use in the Elderly***

No dosage alteration in elderly patients is necessary.

### ***Use in Children***

The safety and effectiveness of TRAVATAN Eye Drops in paediatric patients have not been established.

### ***Hepatic / Renal Impairment***

TRAVATAN Eye Drops have been studied in patients with mild to severe hepatic or renal impairment (creatinine clearance as low as 14mL/min). No dosage alteration is necessary in these patients.

### ***Carcinogenicity, mutagenicity, impairment of fertility***

Travoprost did not cause gene mutation in bacteria or chromosomal aberrations in bone marrow cells of mice and rats. A slight increase in mutation frequency was observed in one or two mouse lymphoma L5178Y assays.

Long term studies in mice and rats at SC doses up to 100mcg/kg/day did not provide any evidence of carcinogenic potential. These doses correspond to exposure levels over 200 times human exposure at the maximum recommended clinical dose (MRCD), based on plasma active drug levels.

### ***Impairment of fertility***

There are no human data on the effects of TRAVATAN Eye Drops on male or female fertility. Travoprost had no effects on mating behaviour or fertility in male and female rats at SC doses up to 10mcg/kg (equivalent to 54 times human exposure at the MRCD), although embryofetal resorption was increased at 10mcg/kg (further information on effects on pregnancy is included under **Use in Pregnancy**).

### ***Effects on ability to drive and use machines***

As with other ophthalmic medications, patients should be advised to exercise caution if they experience transient blurred vision following instillation of eye drops; patients should wait until their vision clears before driving or using machinery.

### ***Instructions for patients***

In accordance with good clinical practice for the administration of eye drops, patients should be instructed to gently occlude the nasolacrimal ducts for two minutes after instillation.

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## **Adverse Effects**

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In clinical studies involving over 800 patients, TRAVATAN Eye Drops were administered once or twice daily as primary or adjunctive therapy (with timolol maleate 0.5%). No serious ophthalmic or systemic adverse events related to TRAVATAN Eye Drops were reported in clinical studies. The most frequently reported treatment-related undesirable effect and local symptom was ocular hyperaemia, up to 46% in pivotal studies (range: 32.5 to 46%).

Tabulated adverse reaction data (considered to be possibly, probably or definitely related to treatment), providing comparisons to placebo and other active comparators (to an incidence of 1% or greater), which have been generated from all clinical studies with TRAVATAN Eye Drops, are provided below.

Uncommon ophthalmic events (incidence <1% and ≥ 0.1%) not detailed in the table below included decreased visual acuity, conjunctivitis, ocular irritation, eyelash lengthening, conjunctival follicles, blepharitis, lid oedema, ocular discharge, corneal pigmentation, conjunctival oedema, browache, conjunctival papillae, ocular fatigue and film.

As with other prostaglandin analogues (class effect), TRAVATAN may gradually change eyelashes in the treated eye(s); these changes were observed in about half of patients in clinical trials and include: increased length, thickness, pigmentation, and/or number of lashes. However, fewer than 1% reported these as adverse events. The mechanism of eyelash changes and their long term consequences are currently unknown.

Uncommon non-ocular events (incidence <1% and ≥ 0.1%) not detailed in the table below included:

Body as a whole:	Asthenia.
Cardiovascular:	Hypotension, bradycardia.
Respiratory:	Rhinitis, pharyngitis.
Skin and appendages:	Erythema, pruritus, periorbital skin discolouration.
Special senses:	Taste perversion
Musculoskeletal:	Myalgia

Tabulated Adverse Reaction Data Comparing Incidence (%) Figures					
Adverse Events	Trav 40	Trav 40 + Tim	Lat	Tim	Placebo
	N = 710	N = 145 <sup>a</sup>	N = 196	N = 727	N = 79 <sup>a</sup>
<b>Ocular</b>					
Hyperaemia	37.3	33.8	24	8.3	-
Discomfort	4.8	3.4	2	4	2.5
Pruritus	5.6	0.7	5.1	1.1	1.3
Pain	3.5	3.4	1.5	0.3	-
Iris discolour	2.1	-	5.1	-	-
Dry eye	1.8	3.4	0.5	0.7	2.5
Foreign body sensation	2	2.1	0.5	0.7	-
Keratitis	1.5	0.7	1.5	1.1	-
Cells	1	4.1	0.5	0.7	-
Flare	1.3	1.4	1	0.4	-
Blurred vision	0.8	0.7	2	0.8	-
Photophobia	1.4	2.8	0.5	0.4	-
Iritis	0.3	0.7	-	0.1	-
Corneal staining	0.1	-	-	-	1.3
Sticky sensation	0.1	1.4	-	-	-
Tearing	0.7	2.1	1.5	0.7	-
<b>Non-ocular</b>					
<u>Body as a whole</u>					
Headache	1.4	-	-	0.3	-
Trav 40 = TRAVATAN 0.004%					
Tim = timolol maleate 0.5%					
Lat = latanoprost 50 mcg/mL					
- = not reported					
<sup>a</sup> Given the low number of patients within these treatment groups, the percentage provided should not be viewed as an accurate reflection of the potential of these adverse events.					

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## Interactions

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The plasma protein binding of the active free acid form of travoprost is moderate (approximately 80%) and, therefore, drug-drug interactions involving protein binding are unlikely.

In clinical studies, TRAVATAN Eye Drops were used concomitantly with timolol or brimonidine eye drops without evidence of additional adverse interactions. Concomitant therapy with miotics or adrenergic agonists has not been evaluated.

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## Overdosage

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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 5,000-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 Eye Drops occurs, treatment should be symptomatic. A topical overdose of TRAVATAN Eye Drops may be flushed from the eyes with warm tap water.

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## Pharmaceutical Precautions

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Store below 25°C. Discard container 4 weeks after opening.

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## Medicine Classification

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Prescription Medicine.

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## Package Quantities

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TRAVATAN Eye Drops 0.004%, containing 40 mcg/mL travoprost, are supplied in 2.5 mL oval DROP-TAINER® dispensers.

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## Further Information

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### *Clinical studies*

Three randomised, double masked, active controlled, parallel, multi-centre studies were conducted to demonstrate the efficacy of TRAVATAN Eye Drops as monotherapy. Table 1 provides summary information from each of these studies. These studies were designed as "non-inferiority" studies, powered to detect a difference of  $\pm 1.5$ mm Hg in intraocular pressure between treatments.

<b>Table 1: Intraocular Pressure Data (mm Hg)</b>						
<b>Treatment (n**)</b>	<b>Baseline</b>			<b>Pressure reduction (Combined* for all visits)</b>		
	<b>8 AM</b>	<b>10 AM</b>	<b>4 PM</b>	<b>8AM</b>	<b>10 AM</b>	<b>4 PM</b>
<b>Study 1 (Data combined across all visits during 12 month study) (95% CI)</b>						
TRAV 40 (197)	26.8 (26.4, 27.2)	25.1 (24.7, 25.5)	24.5 (24.1, 24.9)	-7.7 (-8.1, -7.3)	-7.3 (-7.7, -6.9)	-6.8 (-7.3, -6.4)
TIM (195)	27.0 (26.6, 27.4)	25.4 (25.0, 25.8)	24.6 (24.2, 25.0)	-6.7 (-7.1, -6.4)	-6.0 (-6.4, -5.6)	-5.2 (-5.7, -4.8)
LAT (193)	26.9 (26.4, 27.3)	25.2 (24.8, 25.6)	24.9 (24.5, 25.3)	-7.7 (-8.1, -7.3)	-7.0 (-7.4, -6.7)	-6.4 (-6.9, -5.9)
<b>Study 2<sup>†</sup> (Data combined across all visits during 9 month study) (95% CI)</b>						

<b>Table 1: Intraocular Pressure Data (mm Hg)</b>						
<b>Treatment (n**)</b>	<b>Baseline</b>			<b>Pressure reduction (Combined* for all visits)</b>		
	<b>8 AM</b>	<b>10 AM</b>	<b>4 PM</b>	<b>8AM</b>	<b>10 AM</b>	<b>4 PM</b>
TRAV 40 (197)	27.4 (27.0, 27.8)	26.4 (26.0, 26.9)	25.5 (25.1, 25.9)	-8.6 (-9.0, -8.2)	-8.6 (-9.0, -8.2)	-8.2 (-8.6, -7.7)
TIM (185)	27.1 (26.6, 27.5)	26.2 (25.8, 26.7)	25.1 (24.7, 25.5)	-7.6 (-8.0, -7.3)	-7.5 (-7.9, -7.1)	-6.6 (-7.0, -6.1)
<b>Study 3 (Data combined across all visits during 6 month study) (95% CI)</b>						
TRAV 40 (197)	27.2 (26.8, 27.7)	25.5 (25.1, 26.0)	25.0 (24.5, 25.4)	-7.5 (-8.0, -7.1)	-7.0 (-7.5, -6.6)	-6.9 (-7.4, -6.4)
TIM (199)	27.4 (26.9, 27.8)	25.8 (25.3, 26.2)	25.3 (24.9, 25.8)	-6.8 (-7.2, -6.4)	-6.0 (-6.4, -5.6)	-5.2 (-5.7, -4.7)

\* All reductions were clinically and statistically ( $p = 0.0001$ ) significant compared to baseline.

\*\* Intention to treat. † Morning IOP measurements at 9AM and 11AM

TRAV 40 = TRAVATAN 0.004% nocte, TIM = timolol maleate 0.5% bd, LAT = latanoprost 0.005% nocte

These studies conclusively demonstrate that monotherapy with TRAVATAN Eye Drops produce clinically relevant and statistically significant reductions in intraocular pressure; these reductions in pressure are maintained over a 12-month dosing period.

TRAVATAN Eye Drops was non-inferior to latanoprost Eye Drops 0.005% at all visits during the 12-month study. In addition, an earlier onset of intraocular pressure reduction and better intraocular pressure control throughout the day were observed in patients receiving Travatan Eye Drops, compared to latanoprost Eye Drops 0.005%. However, these were not pre-defined study endpoints and have only been observed in this single study.

TRAVATAN Eye Drops were statistically superior to timolol Eye Drops 0.5% at each IOP measurement time of day, when results were pooled across study visits in the intent-to-treat analysis for each of the 12-month, 9-month, and 6-month studies but was on most occasions within the predetermined 1.5 mm Hg difference in intraocular pressure. Also, TRAVATAN Eye Drops were statistically superior to timolol Eye Drops 0.5% at all visits in the intent-to-treat analysis of the 12-month study, at 11 of 15 visits in the intent-to-treat analysis of the 9-month study, and at 11 of 13 visits in the intent-to-treat analysis of the 6-month study.

TRAVATAN Eye Drops have also been studied as adjunctive therapy. A randomised, double masked, parallel, placebo-controlled, multi centre study, involving 427 patients, was conducted in order to demonstrate the additional intraocular lowering effect of TRAVATAN Eye Drops when added to existing timolol eye drops 0.5% bd. Whilst on timolol alone, the patients had a mean IOP of 24-36 mm Hg at 8am and an IOP of 21-36 mm Hg at 10am and 4pm on 2 days to be assessed as eligible for enrolment. Table 2 provides summary information from this study.

Treatment (n <sup>**</sup> )	8 AM		10 AM		4 PM	
	Mean	95% CI	Mean	95% CI	Mean	95% CI
<b>(Data combined across all visits during 6 month study)</b>						
TRAV 40 (n=137)	19.2	18.6, 19.8	18.1	17.5, 18.7	18.5	17.9, 19.2
Placebo (n=134)	23.8	23.2, 24.4	22.9	22.3, 23.5	22.8	22.1, 23.4
p-value	0.0001		0.0001		0.0001	

\*\* Intention to treat

TRAV 40 = TRAVATAN 0.004%

This study conclusively demonstrates that TRAVATAN Eye Drops produce clinically relevant and statistically significant intraocular pressure reductions, compared to placebo, when used adjunctively with Timolol eye drops 0.5%.

There is limited experience with the use of TRAVATAN Eye Drops in previously untreated patients. In the three pivotal monotherapy studies, the percentage of randomised patients who reported no current glaucoma therapy was 29%. It is not known how many of those patients had received no prior therapy. All patients enrolled in these studies who were on current ocular hypotensive medications underwent a wash out period from 3 days to 3 weeks.

### **Contact Lenses**

If patients continue to wear soft (hydrophilic) contact lenses while under treatment with TRAVATAN Eye Drops they should remove their lens(es) *prior* to instilling TRAVATAN Eye Drops in the affected eye(s) and should not insert their lens(es) until 15 minutes after instillation of the eye drops.

### **List of excipients**

TRAVATAN Eye Drops also contain polyoxyethylene hydrogenated castor oil, disodium edetate, boric acid, trometamol, mannitol and purified water. Each solution is preserved with benzalkonium chloride (0.15 mg/mL).

### **Pharmaceutical**

Travoprost is a clear to slightly opalescent, colourless to yellow oil. Travoprost is practically insoluble in water (approximately 44 ppm).

*Molecular weight:* 500.56

*Empirical formula:* C<sub>26</sub>H<sub>35</sub>F<sub>3</sub>O<sub>6</sub>

*Chemical name:* Isopropyl (Z)-7-[(1R,2R,3R,5S)-3,5-dihydroxy-2-[(1E,3R)-3-hydroxy-4-[(α,α,α-trifluoro- *m*-tolyl)oxy]-1-butenyl]cyclopentyl]-5-heptenoate

*CAS Number:* 157283-68-6

## **Name and Address**

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**Date of Preparation**

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1<sup>st</sup> December 2007

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