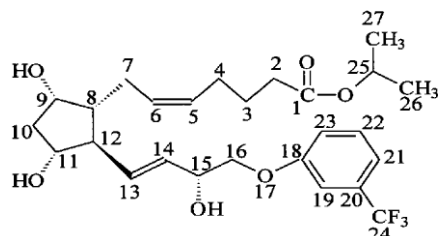


TRAVATAN[®] Z

Travoprost 0.004% Eye Drops

NAME OF THE DRUG

TRAVATAN Z Eye Drops contain travoprost. The chemical structure of travoprost is:



Molecular weight:	500.56
Empirical formula:	C ₂₆ H ₃₅ F ₃ O ₆
Chemical name:	(5Z,13E)-(9S,11R,15R)-9,11,15-Trihydroxy-16- (<i>m</i> -trifluoromethylphenoxy)-17,18,19,20-tetranor-5,13-prostadienoic acid, isopropyl ester
CAS Number:	157283-68-6

DESCRIPTION

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

TRAVATAN Z Eye Drops have been formulated as a sterile solution for topical application to the eye. The buffered aqueous solution has a pH of approximately 6.0 and an osmolality of approximately 290 mOsmol/kg. TRAVATAN Z Eye Drops are preserved in the bottle with an ionic buffered system.

TRAVATAN Z Eye Drops contain 40 µg/mL travoprost, together with boric acid, propylene glycol, polyoxyl 40 hydrogenated castor oil, sorbitol and zinc chloride, sodium hydroxide and/or hydrochloric acid to adjust pH, and purified water, USP.

PHARMACOLOGY

Pharmacokinetics

Travoprost is absorbed into the eye following topical ocular administration where it is hydrolysed to the active free acid. Following administration of 1.2 µg ³H-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 h 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_{2α} 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 travoprost 0.004% Eye Drops, preserved with benzalkonium chloride (BAC), 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.

Pharmacodynamics

Travoprost is an ester prodrug of a PGF_{2α} analogue and is hydrolysed to the active acid. The free acid is a prostaglandin FP receptor agonist. PGF_{2α} 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 2 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 Z 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.

CLINICAL STUDIES

Clinical studies with the BAC-free formulation of TRAVATAN Z 0.004% Eye Drops

One multicentre, randomised, double-masked study of three months duration was conducted to ascertain whether there were any differences in safety and efficacy between the BAC-free formulation of TRAVATAN Z Eye Drops and the initially registered travoprost 0.004% Eye Drops preserved with BAC. Patients (n=690) with open-angle glaucoma or ocular hypertension and baseline pressure of 25–27 mm Hg were treated with BAC-containing travoprost 0.004% or BAC-free TRAVATAN Z once daily in the evening. Both formulations produced statistically significant and clinically relevant reductions in IOP from baseline (see Table 1). Further, this study demonstrated that the two formulations can be considered clinically equivalent, both in terms of efficacy and safety.

Treatment (n ^{**})	Baseline			Pressure reduction (Combined* for all visits)		
	8 AM	10 AM	4 PM	8AM	10 AM	4 PM
TRAV BAC-free (337-338)	27.0 (24-35)	25.5 (21-35)	24.7 (20-35)	-8.4 (-8.5, -8.3, -8.3)	-7.7 (-7.7, -7.7, -7.7)	-7.4 (-7.4, -7.4, -7.3)
TRAV (337-341)	27.2 (24-36)	25.6 (21-35)	24.8 (20-34)	-8.4 (-8.4, -8.3, -8.3)	-7.7 (-7.7, -7.6, -7.8)	-7.5 (-7.4, -7.5, -7.6)

* : All reductions were clinically and statistically (p < 0.0001) significant compared to baseline;

** : Intention to treat;

Both formulations produced statistically significant and clinically relevant reductions in IOP from baseline (see Table 1). when results were pooled across study visits in the intent-to-treat analysis for each of the week 2, week 6 and month 3 time points. Further, this study demonstrated that the two formulations can be considered clinically equivalent, both in terms of efficacy and safety.

The safety and efficacy of the BAC-free formulation of TRAVATAN Z Eye Drops is further supported by the clinical studies reported with BAC-containing travoprost 0.004% Eye Drops.

Clinical studies with BAC-containing travoprost 0.004% Eye Drops.

Three randomised, double masked, active controlled, parallel, multi-centre studies were conducted to demonstrate the efficacy of BAC-containing travoprost 0.004% Eye Drops as monotherapy. Table 2 provides summary information from each of these studies. These studies were designed as “non-inferiority” studies, powered to detect a difference of ± 1.5 mm Hg in intraocular pressure between treatments.

Table 2: Intraocular Pressure Data (mm Hg)						
Treatment (n ^{**})	Baseline			Pressure reduction (Combined* for all visits)		
	8 AM	10 AM	4 PM	8AM	10 AM	4 PM
Study 1 (Data combined across all visits during 12 month study) (95% CI)						
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)
Study 2[†] (Data combined across all visits during 9 month study) (95% CI)						
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)
Study 3 (Data combined across all visits during 6 month study) (95% CI)						
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**: BAC-containing travoprost 0.004% Eye Drops nocte; **TIM**: timolol maleate 0.5% bd; **LAT**: latanoprost 0.005% nocte

Intention to treat; [†]: Morning IOP measurements at 9AM and 11AM; **TRAV 40**: BAC-containing travoprost 0.004% Eye Drops nocte; **TIM**: timolol maleate 0.5% bd; **LAT**: latanoprost 0.005% nocte

These studies conclusively demonstrate that monotherapy with BAC-containing travoprost 0.004% Eye Drops produce clinically relevant and statistically significant reductions in intraocular pressure; these reductions in pressure are maintained over a 12-month dosing period.

BAC-containing travoprost 0.004% Eye Drops were 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 BAC-containing travoprost 0.004% 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.

BAC-containing travoprost 0.004% 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, BAC-containing travoprost 0.004% 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.

BAC-containing travoprost 0.004% Eye Drops have also been studied as adjunctive therapy to timolol and brimonidine. 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 BAC-containing travoprost 0.004% 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 3 provides summary information from this study.

Table 3: Mean Intraocular Pressure Comparison Between BAC-containing Travoprost 0.004% Eye Drops and Placebo (mm Hg)						
Treatment (n ^{**})	8 AM		10 AM		4 PM	
	Mean	95% CI	Mean	95% CI	Mean	95% CI
(Data combined across all visits during 6 month study)						
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: BAC-containing travoprost 0.004% Eye Drops

This study conclusively demonstrates that BAC-containing travoprost 0.004% Eye Drops produce clinically relevant and statistically significant intraocular pressure reductions, compared to placebo, when used adjunctively with timolol eye drops 0.5%.

Additional IOP-lowering efficacy has also been demonstrated when travoprost eye drops is combined with brimonidine eye drops. A multicentre, randomised, double blind, placebo controlled, parallel group study compared travoprost 0.0015% eye drops combined with brimonidine 0.2% eye drops versus travoprost 0.0015% eye drops versus placebo. A total of 81 patients were enrolled into the study and the treatment phase was of 42 days duration. Combined treatment of travoprost with brimonidine 0.2% eye drops produced a statistically significant greater decrease to mean IOP at the 10am time point compared to travoprost eye drops alone. There was a significant fall in IOP compared to placebo for all the travoprost groups.

There is limited experience with the use of BAC-containing travoprost 0.004% 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.

INDICATIONS

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

- ocular hypertension
- open-angle glaucoma

TRAVATAN Z Eye Drops may be used:

- as first line monotherapy
 - as adjunctive therapy
-

CONTRAINDICATIONS

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

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

PRECAUTIONS

OPHTHALMIC USE ONLY

General

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

TRAVATAN Z 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 Z Eye Drops.

TRAVATAN Z 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 Z 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 BAC-containing travoprost 0.004% Eye Drops, macular oedema, including cystoid macular oedema, has been reported during treatment with prostaglandin F_{2α} 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.

Interactions with Other Drugs

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, BAC-containing travoprost 0.004% 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.

Use in Pregnancy

CATEGORY B3

Travoprost and/or its metabolites crossed the placenta in rats. Travoprost was teratogenic in rats at IV doses of 10 µg/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 3 µg/kg/day (29 times the expected human exposure) or in mice at SC doses of up to 0.3 µg/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 1 µg/kg/day (4 times the human exposure) and in rats at IV doses of 10 µg/kg/day. Increased postimplantation loss also occurred in rats at SC doses of 10 µg/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 0.72 µg/kg/day (4 times the expected human exposure), and decreased gestation length and increased stillbirths (see also Use in Lactation) occurred at ≥ 0.12 µg/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 ≥ 0.12 µg/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 Z Eye Drops should stop breast-feeding.

Use in the Elderly

No dosage alteration in elderly patients is necessary.

Use in Children

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

Hepatic / Renal Impairment

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

Carcinogenicity and Mutagenicity.

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 of two mouse lymphoma L5178Y assays.

Long term studies in mice and rats at SC doses up to 100 µg/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 Z 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 10 µg/kg (equivalent to 54 times human exposure at the MRCD), although embryofoetal resorption was increased at 10 µg/kg (further information on effects on pregnancy is included under Use in Pregnancy).

Contact Lenses

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

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.

INFORMATION 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.

ADVERSE REACTIONS

In a controlled clinical study (n=690), a BAC-free formulation of TRAVATAN Z Eye Drops administered once-daily was compared to the formulation of TRAVATAN Eye Drops containing BAC. This study demonstrated a similar adverse event profile for each of the TRAVATAN formulations.

In 344 patients with exposure to the BAC-free formulation of TRAVATAN Z Eye Drops, the most frequently reported treatment-related undesirable effects and local symptoms were ocular hyperemia and ocular pruritus, occurring at an incidence of 5 to 10%. No patient discontinued study participation due to either of these treatment-related adverse events.

Additional treatment-related ocular adverse events reported in patients with exposure to the BAC-free formulation of TRAVATAN Z Eye Drops at an incidence of 1 to 4% included ocular discomfort, ocular dryness, foreign body sensation, ocular pain, and keratitis. Uncommon ocular adverse events (incidence <1% and >0.5%) included lid margin crusting, photophobia, blepharitis, lid erythema, hair disorder (changes in the characteristics of the eyelashes), and lid pruritus. All other treatment-related ocular adverse events were reported in 1 patient each and included allergic reaction, blurred vision, conjunctivitis, conjunctival follicles, corneal erosion, eye fatigue, iritis, and uveitis.

The most frequently reported treatment-related nonocular adverse events reported in patients with exposure to the BAC-free formulation of TRAVATAN Z Eye Drops was periorbital skin discoloration, occurring at an incidence of 0.6%. All other treatment-related nonocular adverse events were reported in 1 patient each and included palpitations, dry mouth, dry nose, and rhinitis.

Additional treatment-related ocular adverse events that have been reported with TRAVATAN Eye Drops containing BAC preservative at an incidence of 1 to 2% and may potentially occur with the preservative free formulation of TRAVATAN Z Eye Drops, include iris discoloration, cells, and flare. Other uncommon ocular events (an incidence of <1% and ≥ 0.1%) include browache, conjunctival oedema, conjunctival papillae, corneal pigmentation, corneal staining, decreased visual acuity, film, lid oedema, ocular discharge ocular irritation, sticky sensation, and tearing, . The most frequent treatment-related nonocular adverse event was headache, occurring at an incidence of 1.4%. Other uncommon nonocular events (an incidence of <1%

and $\geq 0.1\%$) include asthenia, bradycardia, erythema, hypotension, pharyngitis, pruritus, periorbital skin discoloration, myalgia, and taste perversion.

Additional ocular adverse reactions identified from post-marketing experience with TRAVATAN Eye Drops containing BAC preservative include (in alphabetical order) abnormal sensation in the eye, macular edema, and visual disturbance, while nonocular adverse reactions include (in alphabetical order) asthma, dizziness, dyspnea, fatigue, hair color changes, hair growth abnormal, hypersensitivity, hypertension, hypertrichosis, . prostatic specific antigen increased, tachycardia, tinnitus, and vertigo.

DOSAGE & ADMINISTRATION

Instil one drop of TRAVATAN Z 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 Z Eye Drops, discontinue the other agent and start the following day with TRAVATAN Z Eye Drops.

OVERDOSAGE

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 Z Eye Drops occurs, treatment should be symptomatic.

A topical overdose of TRAVATAN Z Eye Drops may be flushed from the eyes with warm tap water.

STORAGE

Store below 25°C.

Discard container 4 weeks after opening.

PRESENTATION

TRAVATAN Z (travoprost) Eye Drops 0.004% is a sterile, isotonic, buffered, aqueous solution of travoprost (0.04 mg/mL) supplied in Alcon's oval DROP-TAINER® package system.

TRAVATAN Z Eye Drops are supplied as a 2.5 mL solution in a 4 mL natural polypropylene dispenser bottle with a natural polypropylene dropper tip and a turquoise polypropylene overcap.

Tamper evidence is provided with a shrink band around the closure and neck area of the package.

NAME AND ADDRESS OF SPONSOR

TRAVATAN Z Eye Drops are supplied in Australia by:

Alcon Laboratories (Australia) Pty Ltd
Unit 10, 25 Frenchs Forest Road East
FRENCHS FOREST NSW 2086

In New Zealand this product is distributed by:

Alcon New Zealand Limited
Auckland New Zealand
Free phone: 0800 101 106

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