NEW ZEALAND DATA SHEET

1. PRODUCT NAME

TRAVATAN™ (travoprost) Eye Drops 0.004%

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL of Travatan Eye Drops contains the active ingredient travoprost 40 μg in 1 mL.

Excipient with known effect

Travatan Eye Drops are preserved with polyquaternium-1.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Eye drops, solution.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Travatan Eye Drops are indicated in adults to decrease elevated intraocular pressure in ocular hypertension and open-angle glaucoma.

Travatan Eye Drops may be used as first line monotherapy or as adjunctive therapy.

4.2. Dose and method of administration

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.

4.3. Contraindications

Travatan Eye Drops are contraindicated in patients with a known hypersensitivity to travoprost or any of the excipients listed under 6.1. List of excipients.

Travatan Eye Drops are also contraindicated in pregnant women or women attempting to become pregnant (see 4.6. Fertility, pregnancy and lactation).

4.4. Special warnings and precautions for use

Not for injection or oral ingestion

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

Eye colour changes

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 eyelid changes

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

Periorbital and lid changes including deepening of the eyelid sulcus have been observed with prostaglandin analogues.

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

Aphakic patients

Macular oedema has been reported during treatment with prostaglandin F2a analogues. Use travoprost with caution in aphakic patients, pseudophakic patients with torn posterior lens capsule or anterior chamber lenses, or in patients with known risk factors for macular oedema.

Iritis / uveitis

There is no experience of Travatan Eye Drops in an 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.

Travatan Eye Drops should be used with caution in patients with active intraocular inflammation, as well as patients with predisposing risk factors for uveitis.

Paediatric use

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

Use in the elderly

No dosage alteration in elderly patients is necessary.

Hepatic / renal impairment

Travatan 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.

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.

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.

4.5 Interactions with other medicinal products and other forms of interactions

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, 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.

4.6 Fertility, pregnancy and lactation

Pregnancy

Category B3

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. Refer to Section 5.3 for pre-clinical reproductive studies on travoprost.

Breast-feeding

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 Eye Drops should stop breast-feeding. Refer to Section 5.3 for pre-clinical studies on travoprost in lactation.

Effects on fertility

There are no human data on the effects of Travatan Eye Drops on male or female fertility. Refer to Section 5.3 for pre-clinical studies on travoprost in fertility.

This medicine has a boron containing excipient. In animal studies, boron has been shown to cause reduced fertility and embryofoetal development effects, and this appears to be dose related. The relevance of this to humans is uncertain. When used as directed (see section 4.2), the use of this medicine is unlikely to exceed the safety threshold for maximum daily boron exposure.

4.7 Effects on ability to drive or 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.

4.8 Undesirable effects

In clinical studies involving over 4600 patients, Travatan Eye Drops preserved with benzalkonium chloride or polyquaternium-1 was administered once daily as monotherapy or adjunctive therapy to timolol 0.5%. No serious ophthalmic or systemic undesirable effects related to Travatan Eye Drops were reported in any of the clinical studies. The most frequently reported treatment-related undesirable effect with Travatan Eye Drops monotherapy was hyperaemia of the eye (21.8%), which included ocular, conjunctival, or scleral hyperaemia. Hyperaemia was mild in 83.8% of those patients who experienced it. Almost all patients (98%) who experienced hyperaemia did not discontinue therapy as a result of this event. In phase III clinical studies ranging from 6 to 12 months in duration, hyperaemia decreased over time.

The following undesirable effects were assessed to be treatment-related with Travatan Eye Drops monotherapy and are classified according to the following convention: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare

(≥1/10,000 to <1/1000), or very rare (<1/10,000). Within each frequency grouping, undesirable effects are presented in decreasing order of seriousness.

System Organ Classification	**MedDRA Preferred Term (v.18.0)**
Eye disorders	*Very common*: conjunctival hyperaemia, ocular hyperaemia, iris hyperpigmentation. *Common* : punctate keratitis, anterior chamber cell, anterior chamber flare, eye pain, photophobia, eye discharge, ocular discomfort, eye irritation, abnormal sensation in eye, foreign body sensation in eyes, visual acuity reduced, vision blurred, dry eye, eye pruritus, lacrimation increased, erythaema of eyelid, eyelid oedema, eyelids pruritis, growth of eyelashes, eyelash discolouration. *Uncommon* : corneal erosion, iridocyclitis, iritis, uveitis, keratitis, anterior chamber inflammation, eye swelling, corneal staining, photopsia, blepharitis, conjunctival oedema, halo vision, conjunctivitis allergic, conjunctival disorder, conjunctivitis, conjunctival follicles, hypoaesthesia eye, ectropion, keratoconjunctivitis sicca, cataract, eye allergy, eyelid pain, eyelid disorder, eyelid margin crusting, scleral hyperaemia, asthenopia.
Infections and infestations	*Uncommon*: herpes simplex.
Immune system disorders	*Uncommon*: hypersensitivity, seasonal allergy.
Nervous system disorders	*Common*: headache. *Uncommon*: dysgeusia, visual field defect.
Cardiac disorders	*Uncommon*: heart rate irregular, palpitations, heart rate decreased.
Vascular disorders	*Uncommon*: blood pressure decreased, blood pressure increased, hypotension.
Respiratory, thoracic and mediastinal disorders	*Uncommon*: dyspnoea, asthma, respiratory disorder, oropharyngeal pain, cough, dysphonia, nasal congestion, throat irritation.

System Organ Classification	MedDRA Preferred Term (v.18.0)
Gastrointestinal disorders	*Uncommon*: peptic ulcer reactivated, gastrointestinal disorder, dry mouth, constipation.
Skin and subcutaneous tissue disorders	*Common*: skin hyperpigmentation (periocular), skin discolouration. *Uncommon*: dermatitis allergic, periorbital oedema, dermatitis contact, erythaema, hair colour changes, hair texture abnormal, hypertrichosis, madarosis.
Musculoskeletal, connective tissue and bone disorders	*Uncommon*: shoulder pain.
General disorders and administration site conditions	*Uncommon*: asthenia, malaise.

Class Effects

As with other prostaglandin analogues, Travatan Eye Drops 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.

Long-Term Clinical Study

In a post approval long-term clinical study of 5 years duration involving 502 patients, travoprost 0.004% Eye Drops preserved with BAK were administered once daily. No serious ophthalmic or systemic undesirable effects related to travoprost 0.004% Eye Drops were reported in the clinical study. The most frequently reported treatment-related undesirable effect with travoprost 0.004% Eye Drops was iris hyperpigmentation (29.5%). Consequently, classification of this effect has been updated from Common to Very Common. The upward change in frequency category does not represent a safety concern but rather presents a more accurate representation of the expected frequency of this effect associated with long-term exposure to a prostaglandin analogue.

Hyperaemia of the eye assessed as related to the use of travoprost 0.004% Eye Drops was reported at an incidence of 10.0% with 2% of patients reporting hyperaemia of the eye discontinuing study participation due to the undesirable effect.

In addition, several new adverse reactions have been identified from this long-term clinical study that have not been reported previously in clinical trials with travoprost 0.004% Eye Drops as monotherapy. All of these effects have been classified as Uncommon (≥1/1,000 to <1/100) and are listed in the table below:

Additional Adverse Drug Reactions Identified from long-term (5-year) Clinical Study

Adverse Drug Reaction*	Frequency
Anterior chamber pigmentation	Uncommon
Corneal epithelium defect	Uncommon
Corneal pigmentation	Uncommon
Dark circles under eyes	Uncommon
Dizziness	Uncommon
Drug hypersensitivity	Uncommon
Eye inflammation	Uncommon
Hypercholesterolaemia	Uncommon
Hypertension	Uncommon
Influenza	Uncommon
Keratitis herpetic	Uncommon
Macular degeneration	Uncommon
Meibomianitis	Uncommon
Metrorrhagia	Uncommon
Mydriasis	Uncommon
Pigment dispersion syndrome	Uncommon
Rash	Uncommon

* MeDRA terminology used

Post Marketing Experience

Adverse reactions identified from post-marketing experience that have not been reported previously in clinical trials with Travatan Eye Drops as monotherapy include the following:

Ocular: macular oedema.

Systemic: bradycardia, tachycardia, aggravated asthma, vertigo, PSA increase, hair growth abnormality.

The following adverse reactions have been reported during post marketing clinical studies in 4081 patients with Travatan Eye Drops and are classified according to the subsequent convention: very common (≥ 1/10), common (≥ 1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000) and very rare (<1/10,000). Within each frequency-grouping, adverse reactions are presented in order of decreasing seriousness.

System Organ Classification	**MedDRA Preferred Term (v.18.0)**
Eye disorders	*Very Common*: ocular hyperaemia. *Common*: eye pain, eye pruritus, dry eye, eye irritation, iris hyperpigmentation, ocular discomfort. *Uncommon*: corneal erosion, punctate keratitis, keratitis, iritis, cataract, visual acuity reduced, conjunctivitis, anterior chamber inflammation, blepharitis, vision blurred, photophobia, periorbital oedema, eyelids pruritus, eye discharge, eyelid margin crusting, lacrimation increased, erythema of eyelid, growth of eyelashes. *Rare*: uveitis, iridocyclitis, ophthalmic herpes simplex, conjunctival follicles, conjunctival oedema, hypoaesthesia eye, eye inflammation, trichiasis, eczema eyelids, anterior chamber pigmentation, asthenopia, eye allergy, eyelid irritation, eyelash hyperpigmentation, eyelash thickening.
Immune system disorders	*Uncommon*: hypersensitivity.
Nervous system disorders	*Uncommon*: headache. *Rare*: dizziness, dysgeusia.
Cardiac disorders	*Rare*: heart rate decreased, palpitations.
Vascular disorders	*Rare*: hypertension.
Respiratory, thoracic and mediastinal disorders	*Rare*: asthma, dyspnoea, dysphonia, cough, rhinitis allergic, oropharyngeal pain, nasal discomfort, nasal dryness.
Gastrointestinal disorders	*Rare*: dry mouth, constipation.
Skin and subcutaneous tissue disorders	*Uncommon*: skin hyperpigmentation, hypertrichosis. *Rare*: skin discolouration, madarosis, hair colour changes, rash.
General disorders and administrative site conditions	*Rare*: asthenia.

Additional adverse reactions identified from post-marketing surveillance include the following. Frequencies cannot be estimated from the available data. Within each System Organ Class adverse reactions are presented in order of decreasing seriousness.

System Organ Classification	**MedDRA Preferred Term (v.18.0)**
Eye disorders	Macular oedema, lid sulcus deepened.
Psychiatric disorders	Depression, anxiety, insomnia.
Ear and labyrinth disorders	Tinnitus.
Cardiac disorders	Arrhythmia, tachycardia, chest pain.
Vascular disorders	Hypotension.
Gastrointestinal disorders	Diarhhoea, vomiting, nausea, abdominal pain,
Skin and subcutaneous tissue disorders	Erythema, pruritus.
Musculoskeletal and connective tissue disorders	Arthralgia, musculoskeletal pain.
Renal and urinary disorders	Dysuria, urinary incontinence.
Investigations	Prostatic specific antigen increased.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting.

4.9 Overdose

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.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764 766).

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Sensory organ; ophthalmologicals, antiglaucoma preparations, ATC Code SO1HA04.

Mechanism of action

Travoprost, a prostaglandin F_2 analogue, is a highly selective full agonist which has a high affinity for the prostaglandin FP receptor, and reduces the intraocular pressure (IOP) by increasing the outflow of aqueous humour via trabecular meshwork and uveoscleral pathways.

Reduction of the IOP in man starts about 2 hours after administration and maximum effect is reached after 12 hours. Significant lowering of IOP can be maintained for periods exceeding 24 hours with a single dose.

The benzalkonium chloride (BAK)-free Travatan Eye Drops showed a similar IOP-lowering effect to the original travoprost 0.004% Eye Drops preserved with BAK in a clinical study in 340 patients with a 12-week treatment period.

Pharmacodynamic effects

Travoprost significantly increased optic nerve head blood flow in rabbits following 7 days of topical ocular administration (1.4 micrograms, once-daily).

Clinical efficacy and safety

Clinical studies with the BAK-free formulation of Travatan Eye Drops

Pharmacokinetics

A single pharmacokinetic study was conducted to compare the systemic pharmacokinetics of the active metabolite travoprost free acid (AL-5848) following topical ocular administration of BAK-free formulation of Travatan Eye Drops and the initially registered travoprost 0.004% Eye Drops preserved with BAK. The systemic pharmacokinetics of AL-5848 were assessed after single- and multiple- dose topical ocular administration. AL-5848 plasma concentrations were below the limit of quantitation (LOQ = 0.0100 ng/mL) in 93.8% of all samples analysed after administration of Travatan Eye Drops, and in 97.5% of all samples analysed after administration of travoprost 0.004% Eye Drops. With such a large proportion of samples below the limit of detection, pharmacokinetic parameters were not calculated. Low plasma concentrations of AL-5848 were consistent with the concentrations seen in studies supporting the registration of travoprost 0.004% Eye Drops.

Efficacy

One randomised, double masked, parallel-group, multi-centre study was conducted to compare the efficacy of BAK-free Travatan Eye Drops and travoprost 0.004% Eye Drops preserved with BAK. Patients (n=371) with open-angle glaucoma or ocular hypertension were treated with Travatan Eye Drops or travoprost 0.004% Eye Drops once daily in the evening. It was found that both products provide equal IOP control over a 24 hour period.

Statistically significant mean reductions from baseline in IOP were observed for both Travatan Eye Drops and travoprost 0.004% Eye Drops at all time points ($p < 0.001$). Mean IOP reductions from baseline ranged from 7.6 to 8.7 mmHg for Travatan Eye Drops and from 7.7 to 9.2mmHg for travoprost 0.004% Eye Drops, corresponding to IOP reductions of 31% to 33%, and 30% to 34%, respectively. The IOP reductions seen with travoprost 0.004% Eye Drops in this study are consistent with its performance in other reported studies.

Travatan Eye Drops and travoprost 0.004% Eye Drops provide comparable IOP control, defined as IOP < 18 mmHg at any time point. The percentage of patients across study time points with IOP < 18 mmHg ranged from 42% to 64% in the Travatan Eye Drops group and from 44% to 62% in the travoprost 0.004% Eye Drops group.

This study also demonstrated that Travatan Eye Drops provides IOP reduction beyond 24 hours post-dose, as shown previously for travoprost 0.004% Eye Drops. The IOP-lowering efficacy of Travatan Eye Drops was shown to be as good as that of travoprost 0.004% Eye Drops up to 60 hours post-dose.

The safety and efficacy of Travatan Eye Drops is further supported by the clinical studies reported with travoprost 0.004% Eye Drops.

Clinical studies with travoprost 0.004% Eye Drops preserved with BAK

Three randomised, double masked, active controlled, parallel, multi-centre studies were conducted to demonstrate the efficacy of travoprost 0.004% 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 ± 1.5 mmHg in intraocular pressure between treatments.

Table 1: Intraocular Pressure Data (mmHg)

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)

Table 1: Intraocular Pressure Data (mmHg)						
Treatment (n)**	**Baseline**			**Pressure reduction (Combined* for all visits)**		
	8 AM	**10 AM**	**4 PM**	**8AM**	**10 AM**	**4 PM**
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 = travoprost 0.004% Eye Drops nocte, TIM = timolol maleate 0.5% Eye Drops bd. LAT = latanoprost 0.005% Eye Drops nocte.

These studies conclusively demonstrate that monotherapy with 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.

Travoprost 0.004% 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 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.

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 mmHg difference in intraocular pressure. Also, 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.

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 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 mmHg at 8am and an IOP of 21-36 mmHg at 10am and 4pm on 2 days to be assessed as eligible for enrolment. Table 2 provides summary information from this study.

Table 2: Mean Intraocular Pressure Comparison Between Travoprost 0.004% Eye Drops and Placebo (mmHg)

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 = travoprost 0.004% Eye Drops

This study conclusively demonstrates that 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 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.

5.2. Pharmacokinetic properties

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 ^{3}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 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.

Distribution

Following topical ocular administration of Travatan Eye Drops to healthy volunteers, low systemic exposure to active free acid was demonstrated. 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.

Metabolism

Metabolism is the major route of elimination of both travoprost and the active free acid. The metabolic pathways of the acid parallel those of endogenous PGF2α 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.

Excretion

Travoprost free acid and its metabolites are mainly excreted by the kidneys. Travatan Eye Drops has been studied in patients with mild to severe hepatic impairment and in patients with mild to severe renal impairment. No dosage adjustment is necessary in these patients.

5.3 Preclinical safety data

Carcinogenicity

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.

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.

Reproductive studies

Studies in animals with travoprost have shown reproductive toxicity. 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 (e.g. 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 post-implantation 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 post-implantation 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 foetal 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 Lactation below) occurred at ≥ 0.12 μg/kg/day (0.65 times the expected clinical exposure).

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.

Fertility studies

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 Pregnancy).

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Travatan Eye Drops preserved with polyquaternium-1

Polyquaternium-1 10 microgram / mL

Polyoxyethylene hydrogenated castor oil

Boric acid

Mannitol

Sodium chloride

Propylene glycol

Sodium hydroxide and/or hydrochloric acid (to adjust pH)

Purified water.

6.2 Incompatibilities

Unknown

6.3 Shelf life

24 months

6.4 Special precautions for storage

Travatan Eye Drops preserved with polyquaternium-1

Store below 30° C.

Discard container 4 weeks after opening.

6.5 Nature and contents of container

Travatan Eye Drops

2.5 mL oval polypropylene bottle.

6.6 Special precautions for disposal

No special requirements for disposal.

7. MEDICINE SCHEDULE

Prescription Only Medicine

8. SPONSOR

Novartis New Zealand Limited

PO Box 99102

Newmarket

Auckland 1149

New Zealand.

Free Phone: 0800 354 335

9. DATE OF FIRST APPROVAL

Travatan Eye Drops (preserved with polyquaternium-1)

4 May 2011

10. DATE OF REVISION OF THE TEXT

11 August 2023

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
2, 6.1, 6.4, 9	Removal of deregistered Travatan (preserved with benzalkonium chloride)
6.5	Removal of trademark DROP-TAINER

® Registered Trademark.

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