

1. NAME OF THE MEDICINAL PRODUCT

TRAVATAN

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL of solution contains 40 micrograms of travoprost.

Excipient(s) with known effect

Each mL of solution contains polyquaternium-1 (POLYQUAD) 10 microgram, propylene glycol 7.5 mg, polyoxyethylene hydrogenated castor oil 40 (HCO-40) 2 mg (see section 4.4.)

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Ophthalmic solution

Colourless to light yellow solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

TRAVATAN Ophthalmic Solution is indicated for the reduction of elevated intra ocular pressure in patients with open-angle glaucoma or ocular hypertension who are intolerant of other intraocular pressure lowering medications or insufficiently responsive (failed to achieve target IOP determined after multiple measurements over time) to another intraocular pressure lowering medication.

4.2 Posology and method of administration

Posology

Use in adults, including elderly population

The dose is one drop of TRAVATAN in the conjunctival sac of the affected eye(s) once daily. Optimal effect is obtained if the dose is administered in the evening.

Nasolacrimal occlusion or gently closing the eyelid after administration is recommended. This may reduce the systemic absorption of medicinal products administered via the ocular route and result in a decrease in systemic adverse reactions.

If more than one topical ophthalmic medicinal product is being used, the medicinal products must be administered at least 5 minutes apart (see section 4.5).

If a dose is missed, treatment should be continued with the next dose as planned. The dose should not exceed one drop in the affected eye(s) daily.

When substituting another ophthalmic antiglaucoma agent with TRAVATAN, the other agent should be discontinued and TRAVATAN should be started the following day.

Hepatic and renal impairment

TRAVATAN has been studied in patients with mild to severe hepatic impairment and in patients with mild to severe renal impairment (creatinine clearance as low as 14 ml/min). No dosage adjustment is necessary in these patients

Method of Administration

For ocular use.

The patient should remove the protective overwrap immediately prior to initial use. To prevent contamination of the dropper tip and solution, care must be taken not to touch the eyelids, surrounding areas or other surfaces with the dropper tip of the bottle.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Eye colour change

TRAVATAN 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 a permanent change in eye colour. 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. 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 eye lid changes

In controlled clinical trials, periorbital and/or eyelid skin darkening in association with the use of TRAVATAN has been reported in 0.4% of patients. Periorbital and lid changes including deepening of the eyelid sulcus have also been observed with prostaglandin analogues.

TRAVATAN may gradually change eyelashes in the treated eye(s); these changes were observed in about half of the patients in clinical trials and include: increased length, thickness, pigmentation, and/or number of lashes. The mechanism of eyelash changes and their long-term consequences are currently unknown.

TRAVATAN has been shown to cause slight enlargement of the palpebral fissure in studies in the monkey. However, this effect was not observed during the clinical trials and is considered to be species specific.

There is no experience of TRAVATAN in inflammatory ocular conditions; nor in neovascular, angle-closure, narrow-angle or congenital glaucoma and only limited experience in thyroid eye disease, in open-angle glaucoma of pseudophakic patients and in pigmentary or pseudoexfoliative glaucoma. TRAVATAN should therefore be used with caution in patients with active intraocular inflammation.

Aphakic patients

Macular oedema has been reported during treatment with prostaglandin F2a analogues. Caution is recommended when using Travatan in aphakic patients, pseudophakic patients with a torn posterior lens capsule or anterior chamber lenses, or in patients with known risk factors for cystoid macular oedema.

Iritis/uveitis

In patients with known predisposing risk factors for iritis/uveitis, TRAVATAN should be used with caution.

Contact with the skin

Skin contact with TRAVATAN must be avoided as transdermal absorption of travoprost has been demonstrated in rabbits.

Prostaglandins and prostaglandin analogues are biologically active materials that 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 the unlikely event of coming in contact with a substantial portion of the contents of the bottle, thoroughly cleanse the exposed area immediately.

Contact lenses

Patients must be instructed to remove contact lenses prior to application of TRAVATAN and wait 15 minutes after instillation of the dose before reinsertion.

Excipients

TRAVATAN contains propylene glycol which may cause skin irritation.
TRAVATAN contains polyoxyethylene hydrogenated castor oil 40 which may cause skin reactions.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

4.6 Fertility, pregnancy and lactation

Women of child-bearing potential/contraception

TRAVATAN must not be used in women of childbearing age/potential unless adequate contraceptive measures are in place (see section 5.3).

Pregnancy

Travoprost has harmful pharmacological effects on pregnancy and/or the fetus/new-born child. TRAVATAN should not be used during pregnancy unless clearly necessary.

Breastfeeding

It is unknown whether travoprost from the eye drops is excreted in human breast milk. Animal studies have shown excretion of travoprost and metabolites in breast milk. The use of TRAVATAN by breast-feeding mothers is not recommended.

Fertility

There are no data on the effects of TRAVATAN on human fertility. Animal studies showed no effect of travoprost on fertility at doses more than 250 times the maximum recommended human ocular dose.

4.7 Effects on ability to drive and use machines

TRAVATAN has no or negligible influence on the ability to drive and use machines, however as with any eye drop, temporary blurred vision or other visual disturbances may affect the ability to drive or use machines. If blurred vision occurs at instillation, the patient must wait until the vision clears before driving or using machines.

4.8 Undesirable effects

Summary of the safety profile

In clinical trials with TRAVATAN, the most common adverse reactions were ocular hyperaemia and iris hyperpigmentation, occurring in approximately 20% and 6% of patients respectively.

Tabulated list of adverse reactions

The following adverse reactions are classified according to the following convention: very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ to $< 1/1,000$), very rare $< 1/10,000$, or not known (frequency cannot be estimated from the available data). Within each frequency group, adverse reactions are presented in decreasing order of seriousness. The adverse reactions were obtained from clinical studies and post- marketing data with TRAVATAN.

System Organ Class	Frequency	Adverse Reactions
Immune system disorders	Uncommon	hypersensitivity, seasonal allergy
Psychiatric disorders	Not known	depression, anxiety, insomnia
Nervous system disorder	Uncommon	headache
	Rare	dizziness, visual field defect, dysgeusia
Eye disorders	Very common	ocular hyperaemia
	Common	iris hyperpigmentation, eye pain, ocular discomfort, dry eye, eye pruritus, eye irritation

	Uncommon	corneal erosion, uveitis, iritis, anterior chamber inflammation, keratitis, punctate keratitis, photophobia, eye discharge, blepharitis, erythema of eyelid, periorbital oedema, eyelids pruritus, visual acuity reduced, vision blurred, lacrimation increased, conjunctivitis, ectropion, cataract, eyelid margin crusting, growth of eyelashes
	Rare	iridocyclitis, ophthalmic herpes simplex, eye inflammation, photopsia, eczema eyelids, conjunctival oedema, halo vision, conjunctival follicles, hypoaesthesia eye, trichiasis, meibomianitis, anterior chamber pigmentation, mydriasis, asthenopia, eyelash hyperpigmentation, eyelash thickening
	Not known	macular oedema, lid sulcus deepened
Ear and labyrinth disorders	Not known	vertigo, tinnitus
Cardiac disorders	Uncommon	palpitations
	Rare	heart rate irregular, heart rate decreased
	Not known	chest pain, bradycardia, tachycardia, arrhythmia
Vascular disorders	Rare	blood pressure diastolic decreased, blood pressure systolic increased, hypotension, hypertension
Respiratory, thoracic and mediastinal disorders	Uncommon	cough, nasal congestion, throat irritation
	Rare	dyspnoea, asthma, respiratory disorder, oropharyngeal pain, dysphonia, rhinitis allergic, nasal dryness
	Not known	asthma aggravated, epistaxis
Gastrointestinal disorders	Rare	peptic ulcer reactivated, gastrointestinal disorder, constipation, dry mouth
	Not known	diarrhoea, abdominal pain, nausea, vomiting
Skin and subcutaneous tissue disorders	Uncommon	skin hyperpigmentation (periocular), skin discolouration, hair texture abnormal, hypertrichosis
	Rare	dermatitis allergic, dermatitis contact, erythema, rash, hair colour changes, madarosis
	Not known	pruritus, hair growth abnormal
Musculoskeletal and connective tissue disorders	Rare	musculoskeletal pain, arthralgia
Renal and urinary disorders	Not known	dysuria, urinary incontinence
General disorders and administration site conditions	Rare	asthenia
Investigations	Not known	prostatic specific antigen increased

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form <https://sideeffects.health.gov.il>

4.9 Overdose

No cases of overdose have been reported. A topical overdose is not likely to occur or to be associated with toxicity. A topical overdose of TRAVATAN may be flushed from the eye(s) with lukewarm water. Treatment of a suspected oral ingestion is symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Ophthalmologicals-antiglaucoma preparations and miotics-prostaglandin analogues, ATC code: S01E E04

Mechanism of action

Travoprost, a prostaglandin F_{2α} analogue, is a highly selective full agonist which has a high affinity for the prostaglandin FP receptor, and reduces the intraocular pressure by increasing the outflow of aqueous humour via trabecular meshwork and uveoscleral pathways. Reduction of the intraocular pressure in man starts about 2 hours after administration and maximum effect is reached after 12 hours. Significant lowering of intraocular pressure can be maintained for periods exceeding 24 hours with a single dose.

Clinical efficacy and safety

In a clinical trial, patients with open-angle glaucoma or ocular hypertension who were treated with TRAVATAN (polyquaternium-preserved) dosed once-daily in the evening demonstrated 8 to 9 mmHg reductions (approximately 33%) in intraocular pressure from 24 to 26 mmHg baseline. Data on adjunctive administration of TRAVATAN with timolol 0.5% and limited data with brimonidine 0.2% were collected during clinical trials that showed an additive effect of TRAVATAN with these glaucoma medications. No clinical data are available on adjunctive use with other ocular hypotensive medications.

Secondary pharmacology

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

TRAVATAN preserved with polyquaternium-1 induced minimal ocular surface toxicity, compared to eye drops preserved with benzalkonium chloride, on cultured human corneal cells and following topical ocular administration in rabbits.

5.2 Pharmacokinetic properties

Absorption

Travoprost is an ester prodrug. It is absorbed through the cornea where the isopropyl ester is hydrolysed to the active free acid. Studies in rabbits have shown peak concentrations of 20 ng/mL of the free acid in aqueous humour one to two hours after topical dosing of TRAVATAN. Aqueous humour concentrations declined with a half-life of approximately 1.5 hours.

Distribution

Following topical ocular administration of TRAVATAN 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-administration. 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.

Biotransformation

Metabolism is the major route of elimination of both travoprost and the active free acid. The systemic metabolic pathways parallel those of endogenous prostaglandin $F_{2\alpha}$ which are characterised by reduction of the 13-14 double bond, oxidation of the 15-hydroxyl and β -oxidative cleavages of the upper side chain.

Elimination

Travoprost free acid and its metabolites are mainly excreted by the kidneys. TRAVATAN has been studied in patients with mild to severe hepatic impairment and in patients with mild to severe renal impairment (creatinine clearance as low as 14 ml/min). No dosage adjustment is necessary in these patients.

5.3 Preclinical safety data

In ocular toxicity studies in monkeys, administration of travoprost at a dose of 0.45 microgram, twice a day, was shown to induce increased palpebral fissure. Topical ocular administration of travoprost to monkeys at concentrations of up to 0.012% to the right eye, twice daily for one year resulted in no systemic toxicity.

Reproduction toxicity studies have been undertaken in rat, mice and rabbit by systemic route. Findings are related to FP receptor agonist activity in uterus with early embryoletality, post-implantation loss, foetotoxicity. In pregnant rat, systemic administration of travoprost at doses more than 200 times the clinical dose during the period of organogenesis resulted in an increased incidence of malformations. Low levels of radioactivity were measured in amniotic fluid and foetal tissues of pregnant rats administered ^3H -travoprost. Reproduction and development studies have demonstrated a potent effect on foetal loss with a high rate observed in rats and mice (180 pg/ml and 30 pg/ml plasma, respectively) at exposures 1.2 to 6 times the clinical exposure (up to 25 pg/ml).

Environmental Risk Assessment (ERA)

Travoprost is considered a persistent, bioaccumulative and toxic (PBT) substance. Hence, despite the very small amounts of travoprost used by patients in eye drops, a risk to the environment cannot be excluded.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Propylene glycol (E1520)
Sodium chloride
Mannitol (E421)
Boric acid (E284)
Polyoxyethylene hydrogenated castor oil 40 (HCO-40)\
Polyquaternium-1 (eq. to Polyquaternium-1)
Sodium hydroxide and/or hydrochloric acid (for pH-adjustment)
Purified water

6.2 Incompatibilities

None known.

Specific *in vitro* interaction studies were performed with TRAVATAN and medicinal products containing thiomersal. No evidence of precipitation was observed.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials

Discard 4 weeks after first opening.

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and content of container

Oval bottle with dispensing plug and screw cap, all polypropylene, presented in an overwrap.
Each bottle contains 2.5 mL of solution.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements. It should be noted that travoprost is considered a PBT substance (see section 5.3).

7. Registration holder and importer's name and address:

Novartis Israel Ltd., P.O.B. 7126, Tel Aviv

8. Registration Number

126 37 30541

Revised in April 2022 according to MoH guidelines.