

1. NAME OF THE MEDICINAL PRODUCT

TRAVATAN®40 micrograms/ml eye drops, solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml of solution contains 40 micrograms of travoprost.

Preservative: 1 ml of solution contains 10 microgram polyquaternium-1 (POLYQUAD®)

Excipients with known effect: 1 ml of solution contains 7.5 mg propylene glycol, 2 mg polyoxyethylene hydrogenated castor oil 40 (HCO-40) (see section 4.4.).

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Eye drops, solution.

Clear, colourless to light yellow solution .

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

TRAVATAN® eye drops contains travoprost, a prostaglandin analogue.

TRAVATAN eye drops is indicated for the decrease in elevated intraocular pressure in patients with ocular hypertension or open-angle glaucoma (see section 5.1).

4.2 Posology and method of administration

Posology

Use in adults, including the elderly population

The dose is 1 drop of TRAVATAN eye drops in the conjunctival sac of the affected eye(s) once daily. Optimal effect is obtained if the dose is administered in the evening.

TRAVATAN should not be administered more than once daily since it has been shown that more frequent administration of prostaglandin analogues may decrease the intraocular pressure lowering effect.

If a dose is missed, treatment should be continued with the next dose as planned. The dose should not exceed 1 drop in the affected eye(s) daily.

TRAVATAN may be used concomitantly with other topical ophthalmic drug products to lower intraocular pressure.

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

Use in children

The efficacy and safety of TRAVATAN eye drops in patients below the age of 18 years have not been established and its use is not recommended in these patients until further data become available.

Use in patients with Hepatic and renal impairment

TRAVATAN eye drops 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. Keep the bottle tightly closed when not in use.

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 product is being used, the products must be administered at least 5 minutes apart. Eye ointments should be administered last.

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 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 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 eye drops has been reported in 0.4 % of patients.
- TRAVATAN eye drops 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.
- Periorbital and lid changes including deepening of the eyelid sulcus have been observed with prostaglandin analogues.
- TRAVATAN eye drops have 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.

Iritis/Uveitis

- There is no experience of TRAVATAN eye drops 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 eye drops should therefore be used with caution in patients with active intraocular inflammation, as well as in patients with known predisposing risk factors for iritis/uveitis.

Aphakic Patients

- Macular oedema has been reported during treatment with prostaglandin $F_{2\alpha}$ analogues. Use TRAVATAN eye drops with caution in aphakic patients, pseudophakic patients with a torn posterior lens capsule or anterior chamber lenses, or in patients with known risk factors for macular oedema.

Others

- Skin contact with TRAVATAN eye drops 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.
- TRAVATAN eye drops contain propylene glycol which may cause skin irritation.
- TRAVATAN eye drops contain polyoxyethylene hydrogenated castor oil 40 which may cause skin reactions.
- Patients must be instructed to remove contact lenses prior to application of TRAVATAN eye drops and wait at least 15 minutes before reinsertion.

4.5 Interaction with other medicinal products and other forms of interaction

No clinically relevant interactions have been described.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/contraception

TRAVATAN eye drops should not be used in women of child bearing age/potential unless adequate contraceptive measures are in place (see section 5.3).

Pregnancy

Travoprost has harmful pharmacological effects on pregnancy and/or the foetus/new-born child. Studies in animals with travoprost have shown reproductive toxicity.

TRAVATAN eye drops should not be used during pregnancy unless clearly necessary.

Breastfeeding

It is unknown whether topical travoprost or its metabolites are excreted in human milk. Animal studies have shown excretion of travoprost and its metabolites in breast milk.

The use of TRAVATAN eye drops by breast-feeding mothers is not recommended.

Fertility

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

4.7 Effects on ability to drive and use machines

Temporary blurred vision or other visual disturbances may affect the ability to drive or use machines. If blurred vision occurs after instillation, the patient must wait until the vision clears before driving or using machinery.

4.8 Undesirable effects

Tabulated summary of adverse reactions

The following adverse reactions have been identified during clinical studies and post-marketing surveillance. The adverse reactions are classified according to the following convention : very common ($\geq 1/10$), common ($> 1/100$ to $< 1/10$), uncommon ($> 1/1,000$ to $\leq 1/100$), rare ($> 1/10,000$ to $\leq 1/1000$), very rare ($\leq 1/10,000$) or not known (cannot be estimated from the available data; data from post-marketing surveillance). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

TRAVATAN® Eye Drops (polyquaternium-1-preserved)

| System Organ Classification | Frequency | MedDRA Preferred Term (v.18.0) |
|-----------------------------|-------------|--|
| Immune system disorders | Uncommon | hypersensitivity |
| Nervous system disorders | Uncommon | Headache, visual field defect |
| | Rare | dizziness, dysgeusia |
| 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, ectropion, 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 edema, hypoaesthesia eye, eye inflammation, trichiasis, , anterior chamber pigmentation, asthenopia, eye allergy, |

| | | |
|--|-----------|--|
| | | eczema eyelids, eyelid irritation, eyelash hyperpigmentation, mydriasis, eyelash thickening |
| | Not known | macular oedema, lid sulcus deepened |
| Cardiac disorders | Rare | heart rate decreased, palpitations |
| Vascular disorders | Rare | Hypertension, hypotension |
| Respiratory, thoracic and mediastinal disorders | Rare | asthma, dyspnea, 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, erythema, hair colour changes, rash |
| Musculoskeletal and connective tissue disorders | Rare | arthralgia, musculoskeletal pain, |
| General disorders and administration site conditions | Rare | asthenia |

Additional adverse reactions identified from post-marketing surveillance with [Travoprost 40 µg/mL Eye Drops, Solution] 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) |
|---|--|
| Psychiatric disorders | depression, anxiety, insomnia |
| Eye disorders | macular oedema, lid sulcus deepened |
| Ear and labyrinth disorders | tinnitus |
| Cardiac disorders | arrhythmia, tachycardia, chest pain, |
| Respiratory, thoracic and mediastinal disorders | epistaxis |
| Gastrointestinal disorders | diarrhea, vomiting, nausea abdominal pain, |
| Skin and subcutaneous tissue disorders | pruritus |
| Renal and urinary disorders | dysuria, urinary incontinence |
| Investigations | prostatic specific antigen increased |

4.9 Overdose

A topical overdose is not likely to be associated with toxicity. Treatment of an accidental 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 $F_{2\alpha}$ analogue, is a highly selective full agonist which has a high affinity for the prostaglandin FP receptor, and is believed to reduce the intraocular pressure(IOP) by increasing the outflow of aqueous humour via trabecular meshwork and uveoscleral pathways. Reduction of IOP in humans starts approximately 2 hours after administration and maximum IOP reduction is reached within 12 hours. Significant lowering of IOP can be maintained for periods exceeding 24 hours with a single dose.

Clinical efficacy and safety

TRAVATAN eye drops dosed once-daily in patients with open-angle glaucoma or ocular hypertension produced significant reductions in (IOP) when used either as primary therapy or adjunctively to TIMOPTIC¹ (timolol maleate ophthalmic solution) 0.5 % dosed twice daily.

As primary therapy, TRAVATAN eye drops, dosed once daily, reduced IOP 7 to 9 mmHg. Stable diurnal IOP reductions were achieved as early as 2 weeks after initiation of therapy and were maintained over 6 to 12 month treatment periods in 3 well-controlled studies. The IOP reductions with TRAVATAN eye drops were superior to those obtained with TIMOPTIC and equal or better than those obtained with XALATAN¹ (latanoprost ophthalmic solution) 0.005 %dosed once daily. TRAVATAN eye drops demonstrated an earlier stabilization of IOP reduction and better IOP control throughout the day compared to XALATAN 0.005 %. TRAVATAN eye drops was significantly more effective (up to 1.4 mmHg) than XALATAN 0.005 % in reducing IOP in black patients.

A responder analysis (IOP reduction $\geq 30\%$ or mean IOP ≤ 17 mmHg) demonstrated that TRAVATAN eye drops had a significantly higher responder rate (56 %) compared to XALATAN (50 %) and which were both significantly greater than TIMOPTIC (40 %).

In a 6-month well-controlled study, TRAVATAN eye drops dosed once daily adjunctively to TIMOPTIC¹ 0.5 % dosed twice daily provided additional clinically significant IOP reductions (6 to 7 mmHg).

In a clinical trial, patients with open-angle glaucoma or ocular hypertension who were treated with TRAVATAN eye drops (polyquaternium-preserved) dosed once-daily in the evening demonstrated 8 to 9 mmHg reductions (approximately 33 %) in IOP from a baseline range of 24 to 36 mmHg

Data on adjunctive administration of TRAVATAN eye drops with timolol 0.5 % and limited data with brimonidine 0.2 % collected during clinical trials showed an additive effect of TRAVATAN eye drops with these concomitant glaucoma medications. No clinical data are available on adjunctive use with other ocular hypotensive medications.

TRAVATAN eye drops is generally well-tolerated and safe. The most common side effect is hyperaemia, as observed with other ophthalmic prostaglandin analogues.

Pharmacodynamic effects

In addition to reducing IOP, travoprost has been shown to increase optic nerve head blood flow based on data in rabbits following 7 days of topical ocular administration (1.4 micrograms, once daily) and decrease tear film stability and tear secretion. Topical travoprost does not affect respiration rate/volume or systolic blood pressure during exercise and recovery.

TRAVATAN eye drops 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.

In a clinical trial, patients with open-angle glaucoma or ocular hypertension who were treated with Travoprost 0.004% eye drops (polyquaternium-preserved) dosed QD in the evening demonstrated 8-9 mmHg reductions (approximately 33%) in IOP from a baseline range of 24-36 mmHg. Data on adjunctive administration of Travoprost 0.004% eye drops with timolol 0.5% and limited data with brimonidine 0.2% collected during clinical trials showed an additive effect of Travoprost 0.004% eye drops with these concomitant medications. No clinical data are available on adjunctive use with other ocular hypotensive medications. Travoprost 0.004% eye drops is generally well-tolerated and safe. The most common side effect is hyperemia, as observed with other ophthalmic prostaglandin analogs.

5.2 Pharmacokinetic properties

Absorption

Travoprost is an isopropyl ester prodrug. It is absorbed through the cornea where the ester is hydrolysed to the active free acid. Studies in rabbits have shown maximum concentrations of approximately 20 ng/g of travoprost free acid in aqueous humour were achieved within 1 to 2 hours of topical dosing. Aqueous humour concentrations of travoprost free acid declined with a half-life of approximately 1.5 hours. Low concentrations of travoprost free acid are also found in plasma following topical dosing.

Distribution

Following topical ocular administration to humans, low systemic exposure to active free acid was observed, with peak active free acid plasma concentrations of about 25 pg/ml or less observed between 10 and 30 minutes post-dose. Plasma concentrations declined rapidly to below the 10 pg/ml assay quantitation limit within 1 hour of administration.

Biotransformation

Metabolism is the major route of clearance for both travoprost and its free acid. The systemic metabolic pathways parallel those of endogenous prostaglandin F_{2α} which are characterised by reduction of the 13-14 double bond, oxidation of the 15-hydroxyl to a ketone and β-oxidative cleavages of the carboxylic acid side chain.

Elimination

The systemic pharmacokinetics of TRAVATAN eye drops have been studied in patients with mild to severe hepatic impairment as well as in patients with mild to severe renal impairment (creatinine clearance as low as 14 ml/min). No dosage adjustment is required in these populations.

Travoprost free acid and its metabolites are mainly excreted by the kidneys.

Linearity/non-linearity

Travoprost exhibits linear pharmacokinetics in both ocular tissues and plasma after topical ocular administration.

Pharmacokinetic/pharmacodynamic relationship(s)

Pharmacokinetic and Pharmacodynamics relationship has not been established for travoprost after topical ocular administration.

Pharmacokinetic in special populations

The systemic pharmacokinetics of Travoprost 0.004% eye drops has been studied in patients with mild to severe hepatic impairment as well as in patients with mild to severe renal impairment (creatinine clearance as low as 14 mL/minute). No dose adjustment is required in these populations.

Pediatric Pharmacokinetic

The systemic pharmacokinetics of travoprost after topical ocular administration in patients between the ages of 2 months to less than 18 years of age showed a similar concentration range to that of adults, with most plasma samples below the limit of quantitation of 10 pg/mL.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated-dose toxicity, genotoxicity and carcinogenic potential.

Adverse reproductive and developmental toxicity was observed in animals at exposure levels of travoprost similar to clinical exposure levels and is possibly related to clinical use.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

6.2 Incompatibilities

None known.

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

6.3 Shelf Life

Up to 2 years/24 months for 2.5 mL
Up to 12 months for 1.5 mL

6.4 Special precautions for storage

Do not store above 30°C.
Do not use this medicine after the expiry date which is stated on the packaging.
Discard 4 weeks after first opening.
Keep this medicine out of the sight and reach of children.

6.5 Nature and contents of container

Oval bottle containing 1.5 ml or 2.5 ml with dispensing plug and screw cap, all plastic, presented in an overwrap.

Carton containing 1 bottle.

6.6 Instructions for Use and Handling <and Disposal>

No special requirements.

Any unused product or waste material should be disposed of in accordance with local requirements.

6.7 7 Manufacturer

See folding box

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Novartis Pharma AG, Basel, Switzerland