1. NAME OF THE MEDICINAL PRODUCT

TRAVATAN® 40 micrograms/ml eye drops, solution
(travoprost)

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 the 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 or 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. 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

- 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 be become more brownish. After discontinuation of therapy, no further increase in brown iris pigment has been observed.
- 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 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 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.

- 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.
- 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 contains propylene glycol which may cause skin irritation.
- TRAVATAN eye drops contains 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 interaction studies have been performed. However, no clinically relevant interactions are expected to occur.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/contraception
TRAVATAN eye drops should 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 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.

Breast-feeding
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

TRAVATAN eye drops has no or negligible influence on the ability to drive and use machines.

However, 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

Summary of the safety profile
In clinical trials with TRAVATAN eye drops, the most common adverse reactions were ocular hyperaemia and iris hyperpigmentation, occurring in approximately 11% and 5% of patients, respectively.

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 (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1000), very rare (<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.

System organ class	Frequency	Adverse reactions
Immune system disorders	Uncommon	hypersensitivity, seasonal allergy
Psychiatric disorders	Not known	depression, anxiety, insomnia
Nervous system disorders	Uncommon Rare	headache dizziness, dysgeusia
Eye disorders	Very common Common Uncommon Rare Not known	ocular hyperaemia eye pain, eye pruritus, dry eye, eye irritation, iris hyperpigmentation, ocular discomfort 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 uveitis, iridocyclitis, ophthalmic herpes simplex, conjunctival follicles, conjunctival oedema, hypoaesthesia eye, eye inflammation, trichiasis, anterior chamber pigmentation, asthenopia, eye allergy, eczema eyelids, eyelid irritation, eyelash hyperpigmentation, eyelash thickening macular oedema, lid sulcus deepened
Ear and labyrinth disorders	Not known	vertigo, tinnitus
Cardiac disorders	Rare Not known	heart rate decreased, palpitations arrhythmia, chest pain, tachycardia, bradycardia
Vascular disorders	Rare	hypertension, hypotension
Respiratory, thoracic and mediastinal disorders	Uncommon Rare Not known	nasal congestion, throat irritation asthma, dyspnoea, dysphonia, cough, rhinitis allergic, oropharyngeal pain, nasal discomfort, nasal dryness epistaxis
Gastrointestinal disorders	Rare Not known	dry mouth, constipation diarrhoea, vomiting, nausea, abdominal pain

Skin and subcutaneous tissue disorders	Uncommon Rare Not known	skin hyperpigmentation (periocular), hypertrichosis, hair texture abnormal skin discolouration, madarosis, erythema, hair colour changes, rash pruritus, hair growth abnormal
Musculoskeletal and connective tissue disorders	Rare	arthralgia, musculoskeletal pain
Renal and urinary disorders	Not known	dysuria, urinary incontinence
General disorders and administration site conditions	Rare	asthenia
Investigations	Not known	prostatic specific antigen increased

4.9 Overdose

A topical overdose of TRAVATAN eye drops may be flushed from the eye(s) with lukewarm water.

A topical overdose is not likely to occur or to be associated with toxicity. Treatment of an accidental ingestion is symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antiglaucoma preparations and miotics, prostaglandin analogues. ATC code: S01EE04.

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 reduces 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.

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.

Data from clinical trials
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 TIMOPTIC[1] (timolol maleate ophthalmic solution) 0.5% dosed twice daily. The IOP reductions with TRAVATAN eye drops were superior to those obtained with TIMOPTIC and equal or better than those obtained with XALATAN[2] (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 ≥ 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 TIMOPTIC 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 7 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. Travoprost does not affect respiration rate/volume or systolic blood pressure during exercise and recovery. Prostaglandin $F_{2\alpha}$ analogues can induce the anagen phase in hair follicles and stimulate melanogenesis in the skin.

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.

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 that maximum concentrations of approximately 20 ng/ml of travoprost free acid in aqueous humour were achieved within 1 to 2 hours of topical ocular 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 free acid plasma concentrations of about 25 pg/ml or less observed between 10 and 20 minutes post-dose. Plasma concentrations declined rapidly to below the 10 pg/ml assay quantitation limit within 1 hour of administration. Trace plasma concentrations of travoprost may be present immediately following dosing in some subjects.

Biotransformation
Metabolism is the major route of clearance for both travoprost and its free acid in non-clinical species. 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 to a ketone and β-oxidative cleavages of the carboxylic acid side chain.

Elimination
Following administration of radiolabelled travoprost to rats, approximately 95% of the dose was eliminated within 24 hours. Approximately, 75% of the dose was eliminated in the faeces and the remainder excreted in urine.

Linear/non-linear pharmacokinetics
Travoprost exhibits linear pharmacokinetics in both ocular tissues and plasma after topical ocular administration.

Pharmacokinetic/pharmacodynamic relationship(s)
Pharmacokinetic and pharmacodynamic relationship has not been established for travoprost after topical ocular administration.

Pharmacokinetics in special populations
The systemic pharmacokinetics of TRAVATAN 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.

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 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.

6.4 Nature and contents of container

Oval bottle containing 2.5 ml with dispensing plug and screw cap, all plastic, presented in an overwrap.
Carton containing 1 bottle.

6.5 Special precautions for disposal

No special requirements.

[1]TIMOPTIC is a registered trademark of Merck.
[2]XALATAN is a registered trademark of Pfizer.

Manufactured by:
ALCON-COUVREUR
B-2870 Puurs (Belgium) for Novartis Pharma AG, Basel, Switzerland