NOVARTIS SOUTH AFRICA (PTY) LTD
TRAVATAN eye drops, solution
Travoprost 40 µg/ml
PI Approved: 06 June 2014

SCHEDULING STATUS: S4

PROPRIETARY NAME AND DOSAGE FORM:
TRAVATAN® Eye Drops, solution (0,004 %)

COMPOSITION
TRAVATAN® contains 40 µg of travoprost per ml in a sterile ophthalmic solution, preserved with polyquaternium-1 (POLYQUAD) 0,001 % (m/v).
Excipients: boric acid (E284), mannitol (E421), polyoxyethylene hydrogenated castor oil 40 (HCO-40), propylene glycol, sodium chloride, sodium hydroxide and/or hydrochloric acid (to adjust pH) and purified water.

PHARMACOLOGICAL CLASSIFICATION
A.15.4 Ophthalmic preparations, other.
ATC code: S01EX

PHARMACOLOGICAL ACTION
Pharmacodynamic properties:
Travoprost, a prostaglandin $F_{2\alpha}$ analogue, is a selective agonist with an affinity for the prostaglandin FP-receptor. The exact mechanism of action by which travoprost reduces IOP has not been fully elucidated. Travoprost is believed to increase uveoscleral outflow.
Pharmacokinetic properties:
Travoprost is an ester prodrug. It is absorbed through the cornea where the isopropyl ester is hydrolysed to the free acid. 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.
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 within 30 minutes post-dose. Thereafter, plasma levels declined rapidly. 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.

INDICATIONS
Reduction of elevated intraocular pressure in patients with open-angle glaucoma or other ocular hypertension as monotherapy or as adjunctive therapy.
Safety and efficacy beyond three months has not been established.

CONTRA-INDICATIONS
Hypersensitivity to travoprost or any of the excipients of **TRAVATAN®**.
Pregnant women or women attempting to become pregnant, as teratogenicity has been demonstrated in experimental animals.
Breast-feeding women.
Children, as safety and efficacy has not been proven.
Use in children and adolescents:
The efficacy and safety of **TRAVATAN®** Eye Drops in patients below the age of 18 have not been established and its use is not recommended in these patients until further data becomes available.
Women of childbearing potential:

TRAVATAN® must not be used in women who may become pregnant unless adequate contraceptive measures are in place.

Nursing women:

Animal studies indicate that travoprost and its metabolites may pass into breast milk and **TRAVATAN®** must therefore not be used in breast-feeding women.

WARNINGS

TRAVATAN® has been reported to cause changes to pigmented tissues. The most frequently reported changes have been increased pigmentation of the iris and periorbital tissue (eyelid) and increased pigmentation and growth of eyelashes. These changes may be permanent.

TRAVATAN® may gradually change eye colour, increasing the amount of brown pigmentation in the iris by increasing the number of melanosomes (pigment granules) in melanocytes. The long-term effect on the melanocytes and the consequences of potential injury to the melanocytes and/or deposition of pigment granules to other areas of the eye are currently unknown. The change in iris colour occurs slowly and may not be noticeable for months to years. Patients should be informed of the possibility of iris colour change.

Eyelid skin darkening has been reported in association with the use of **TRAVATAN®**.

TRAVATAN® may gradually change eyelashes in the treated eye; these changes include increased length, thickness, pigmentation and/or number of eyelashes.

Patients who are expected to receive treatment in only one eye should be informed about the potential for increased brown pigmentation of the iris, periorbital and/or eyelid tissue and eyelashes of the treated eye, and thus heterochromia between the eyes. They should also be advised of the potential for a disparity between the eyes in length, thickness and/or number of eyelashes.

TRAVATAN® contains propylene glycol which may cause skin irritation.

TRAVATAN® contains polyoxyethylene hydrogenated castor oil 40 (HCO-40) which may cause skin irritation.

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

INTERACTIONS

Interaction with other medicinal products and other forms of interaction:

Data on adjunctive administration of **TRAVATAN®** with timolol and with brimonidine eye drops confirmed the additive effect of **TRAVATAN®** with these glaucoma medications. No data are available on adjunctive use with other ocular hypotensive medications. Data on concomitant administration with brimonidine are limited. Interactions of **TRAVATAN®** with other medications have not been specifically evaluated.

PREGNANCY AND LACTATION

Please refer to the **CONTRA-INDICATIONS** section.

DOSAGE AND DIRECTIONS FOR USE

For ocular use:

The recommended dose in adults and the elderly: one drop of **TRAVATAN®** in the conjunctival sac of the affected eye(s) once daily 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 medicines must be administered at least 5 minutes apart.

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®**, discontinue the other agent and start the following day with **TRAVATAN®**.

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:

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.

Instructions for use and handling:

The patient should remove the protective over-wrap immediately prior to initial use.
Since **TRAVATAN®** is a biologically active material and since it 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 case of accidental contact with the contents of the bottle, thoroughly cleanse the exposed area immediately.

SIDE EFFECTS AND SPECIAL PRECAUTIONS

Side effects:

In 2 clinical trials involved in the development of **TRAVATAN®** (polyquaternium-1-preserved), 201 patients were exposed for up to 3 months. The most frequently reported treatment-related undesirable effect with **TRAVATAN®** (polyquaternium-1 preserved) was hyperaemia of the eye (18,9 %), which included ocular or conjunctival hyperaemia. One patient (0,5 %) discontinued study.
The following undesirable effects were assessed to be treatment-related with **TRAVATAN®** monotherapy and are classified according to the following convention: very common (≥ 1/10); common (≥ 1/100, < 1/10); uncommon (≥ 1/1 000, < 1/100); rare (≥ 1/10 000, < 1/1 000); very rare (≤ 1/10 000). Within each frequency grouping, undesirable effects are presented in decreasing order of seriousness.

Infections and infestations:
Uncommon: herpes simplex, keratitis herpetic.

Immune system disorders:
Uncommon: hypersensitivity, drug hypersensitivity, seasonal allergy.

Nervous system disorders:
Uncommon: dysgeusia, dizziness, visual field defect, headache.

Eye disorders:
Very common: ocular hyperaemia, conjunctival 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, vision blurred, dry eye, eye pruritus, erythema of eyelid, eyelid oedema, growth of eyelashes, eyelash discolouration.
Uncommon: visual acuity reduced, macular degeneration, corneal erosion, iridocyclitis, iritis, uveitis, keratitis, anterior chamber inflammation, eye inflammation, eye swelling, corneal staining, photopia, blepharitis, conjunctival oedema, corneal epithelium defect, halo vision, corneal pigmentation, conjunctivitis allergic, conjunctival disorder, conjunctivitis, conjunctival follicles, hypoaesthesia eye, meibomianitis, lacrimation increased, ectropion, keratoconjunctivitis sicca, sicca syndrome, pigment dispersion syndrome, anterior chamber pigmentation, mydriasis, cataract, eye allergy, eyelid pain, dark circles under eyes, eyelid disorder, eyelid margin crusting, scleral hyperaemia, asthenopia, eyelids pruritus.

Cardiac disorders:

Uncommon: heart rate irregular, palpitations, heart rate decreased.
Vascular disorders:
Uncommon: blood pressure decreased, blood pressure increased, hypotension, hypertension.
Respiratory, thoracic and mediastinal disorders:
Uncommon: dyspnoea, asthma, respiratory disorder, oropharyngeal pain, cough, dysphonia, nasal congestion, throat irritation.
Gastrointestinal disorders:
Uncommon: peptic ulcer reactivated, gastrointestinal disorder, constipation dry mouth
Skin and subcutaneous tissue disorders:
Common: skin hyperpigmentation (periocular).
Uncommon: dermatitis allergic, periorbital oedema, dermatitis contact, erythema, rash, hair colour changes, hair texture abnormal, hypertrichosis, madarosis.
Musculoskeletal, connective tissue and bone disorders:
Uncommon: musculoskeletal pain.
General disorders and administrative site conditions:
Uncommon: asthenia, malaise.

Special precautions:
There have been reports of bacterial keratitis associated with the use of multiple-dose containers of topical ophthalmic products. These containers had been inadvertently contaminated by patients who, in most cases, had a concurrent corneal disease or a disruption of the epithelial surface (see the **HOW TO USE TRAVATAN®** section of the Patient Information Leaflet).
Patients may slowly develop increased brown pigmentation of the iris. This change may not be noticeable for months to years (see Warnings). Iris pigmentation changes may be more noticeable in patients with mixed-coloured irises, i.e. blue-brown, grey-brown**,** yellow-brown and green-brown; however, it has also been observed in patients with brown eyes. The colour change is believed to be due to increased melanin content in the stromal melanocytes of the iris. The exact mechanism of action is unknown at this time. 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. Until more information about increased brown pigmentation is available, patients should be examined regularly, and depending on the situation, treatment may be stopped if increased pigmentation ensues.
TRAVATAN® should be used with caution in patients with active intraocular inflammation (iritis/uveitis).
Macular oedema, including cystoid macular oedema, has been reported during treatment with **TRAVATAN®**. 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. **TRAVATAN®** should be used with caution in these patients.
TRAVATAN® has not been evaluated for the treatment of angle closure, inflammatory or neovascular glaucoma.
Treatment with **TRAVATAN®** may lead to exacerbation of asthma. **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.
TRAVATAN® should not be administered while wearing contact lenses. Contact lenses should be removed prior to the administration of **TRAVATAN®** and may be reinserted 15 minutes following administration.
TRAVATAN® contains **hydrogenated castor oil** and **propylene glycol** which may cause skin reactions and irritation.
Effects on the ability to drive or operate machinery:

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 machinery.

KNOWN SYMPTOMS OF OVERDOSE AND PARTICULARS OF ITS TREATMENT
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 suspected oral ingestion is symptomatic and supportive. If overdosage with **TRAVATAN®** occurs, treatment should be symptomatic.

IDENTIFICATION
Clear, colourless to pale yellow solution.

PRESENTATION
4 ml oval bottle containing 2,5 ml solution, with dispensing plug and screw cap, all polypropylene, placed into a pouch.

STORAGE INSTRUCTIONS
Store at or below 25 °C.
DO NOT USE MORE THAN 30 DAYS AFTER OPENING.
KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER: 36/15.4/0333

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