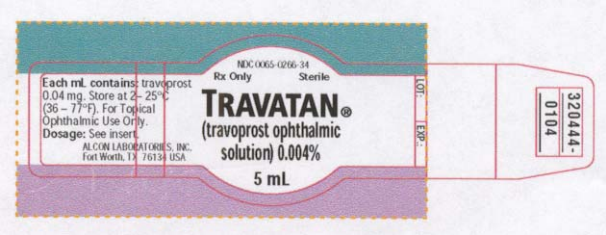
5 ML FILL CONTAINER AND CARTON LABELING:

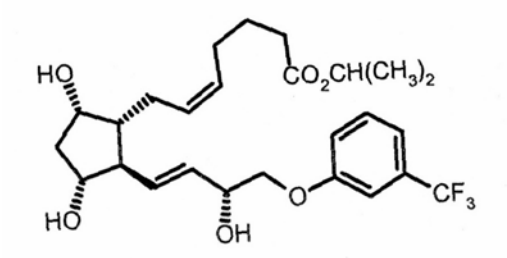


PACKAGE INSERT LABELING:

TRAVATAN® (travoprost ophthalmic solution) 0.004% Sterile

DESCRIPTION

Travoprost is a synthetic prostaglandin $F_{2\alpha}$ analogue. Its chemical name is isopropyl (Z)-7-[(1R,2R,3R,5S)-3,5-dihydroxy-2-[(1E,3R)-3-hydroxy-4-[(α,α,α- trifluoro-m-tolyl)oxy]-l-butenyl]cyclopentyl]-5-heptenoate. It has a molecular formula of $C_{26}H_{35}F_3O_6$ and a molecular weight of 500.56. The chemical structure of travoprost is:



Travoprost is a clear, colorless to slightly yellow oil that is very soluble in acetonitrile, methanol, octanol, and chloroform. It is practically insoluble in water.

TRAVATAN® Ophthalmic Solution 0.004% is supplied as sterile, buffered aqueous solution of travoprost with a pH of approximately 6.0 and an osmolality of approximately 290 mOsmol/kg.

Each mL of TRAVATAN® 0.004% contains 40 *u*g travoprost. Benzalkonium chloride 0.015% is added as a preservative. Inactive Ingredients are: polyoxyl 40 hydrogenated castor oil, tromethamine, boric acid, mannitol, edetate disodium, sodium hydroxide and/or hydrochloric acid (to adjust pH) and purified water.

CLINICAL PHARMACOLOGY

Mechanism of Action

Travoprost free acid is a selective FP prostanoid receptor agonist which is believed to reduce intraocular pressure by increasing uveoscleral outflow. The exact mechanism of action is unknown at this time.

Pharmacokinetics/Pharmacodynamics

Absorption: Travoprost is absorbed through the cornea and is hydrolyzed to the active free acid. Data from four multiple dose pharmacokinetic studies (totaling 107 subjects) have shown that plasma concentrations of the free acid are below 0.01 ng/ml (the quantitation limit of the assay) in two-thirds of the subjects. In those individuals with quantifiable plasma concentrations (N=38), the mean plasma Cmax was 0.018 ± 007 ng/ml (ranged 0.01 to 0.052 ng/mL) and was reached within 30 minutes. From these studies, travoprost is estimated to have a plasma half-life of 45 minutes. There was no difference in plasma concentrations between Days 1 and 7, indicating steady-state was reached early and that there was no significant accumulation.

Metabolism: Travoprost, an isopropyl ester prodrug, is hydrolyzed by esterases in the cornea to its biologically active free acid. Systemically, travoprost free acid is metabolized to inactive metabolites via beta-oxidation of the α(carboxylic acid) chain to give the 1,2-dinor and 1,2,3,4-tetranor analogs, via oxidation of the 15-hydroxyl moiety, as well as via reduction of the 13,14 double bond.

Elimination: The elimination of travoprost free acid from plasma was rapid and levels were generally below the limit of quantification within one hour after dosing. The terminal elimination half-life of travoprost free acid was estimated from fourteen subjects and ranged from 17 minutes to 86 minutes with the mean half-life of 45 minutes. Less than 2% of the topical ocular dose of travoprost was excreted in the urine within 4 hours as the travoprost free acid.

Clinical Studies

In clinical studies, patients with open-angle glaucoma or ocular hypertension and baseline pressure of 25 - 27 mmHg who were treated with TRAVATAN® Ophthalmic Solution 0.004% dosed once-daily in the evening demonstrated 7 - 8 mmHg reductions in intraocular pressure. In subgroup analyses of these studies, mean IOP reduction in black patients was up to 1.8 mmHg greater than in non-black patients. It is not known at this time whether this difference is attributed to race or to heavily pigmented irides.

In a multi-center, randomized, controlled trial, patients with mean baseline intraocular pressure of 24 - 26 mmHg on TIMOPTIC* 0.5% BID who were treated with TRAVATAN® 0.004% dosed QD adjunctively to TIMOPTIC* 0.5% BID demonstrated 6 - 7 mmHg reductions in intraocular pressure.

TRAVATAN® has been studied in patients with hepatic impairment and also in patients with renal impairment. No clinically relevant changes in hematology, blood chemistry, urinalysis laboratory data were observed in these patients.

INDICATIONS AND USAGE

TRAVATAN® Ophthalmic Solution is indicated for the reduction of elevated intraocular 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.

CONTRAINDICATIONS

TRAVATAN® is contraindicated in patients with hypersensitivity to travoprost, benzalkonium chloride or any other ingredients in this product.

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 color, increasing the amount of brown pigmentation in the iris by increasing the number of melanosomes (pigment granules) in melanocytes. The long term effects 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 color occurs slowly and may not be noticeable for months to years. Patients should be informed of the possibility of iris color 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 lashes.

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 in 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.

PRECAUTIONS

General

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 cornea1 disease or a disruption of the epithelial surface (see Information for Patients).

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 colored irides, i.e., blue-brown, grey-brown, yellow-brown, and green-brown; however, it has also been observed in patients with brown eyes. The color 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 a history of intraocular inflammation (iritis/uveitis) and should generally not be used in patients with active intraocular inflammation.

Macular edema, including cystoid macular edema, has been reported during treatment with prostaglandin $F_{2\alpha}$ analogues. 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 edema. TRAVATAN® should be used with caution in these patients.

TRAVATAN® has not been evaluated for the treatment of angle closure, inflammatory or neovascular glaucoma.

TRAVATAN® Ophthalmic Solution should not be administered while wearing contact lenses.

Patients should be advised that TRAVATAN® contains benzalkonium chloride which may be absorbed by contact lenses. Contact lenses should be removed prior to the administration of the solution. Lenses may be reinserted 15 minutes following administration of TRAVATAN®.

Information for Patients

Patients should be advised concerning all the information contained in the Warnings and Precautions sections.

Patients should also be instructed to avoid allowing the tip of the dispensing container to contact the eye or surrounding structures because this could cause the tip to become contaminated by common bacteria known to cause ocular infections. Serious damage to the eye and subsequent loss of vision may result from using contaminated solutions.

Patients also should be advised that if they develop an intercurrent ocular condition (e.g., trauma, or infection) or have ocular surgery, they should immediately seek their physician's advice concerning the continued use of the multi-dose container.

Patients should be advised that if they develop any ocular reactions, particularly conjunctivitis and lid reactions, they should immediately seek their physician's advice.

If more than one topical ophthalmic drug is being used, the drugs should be administered at least five (5) minutes apart.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Two-year carcinogenicity studies in mice and rats at subcutaneous doses of 10, 30, or 100 µg/kg/day did not show any evidence of carcinogenic potential. However, at 100 µg/kg/day, male rats were only treated for 82 weeks, and the maximum tolerated dose (MTD) was not reached in the mouse study. The high dose (100 µg/kg) corresponds to exposure levels over 400 times the human exposure at the maximum recommended human ocular dose (MRHOD) of 0.04 µg/kg, based on plasma active drug levels. Travoprost was not mutagenic in the Ames test, mouse micronucleus test and rat chromosome aberration assay. A slight increase in the mutant frequency was observed in one of two mouse lymphoma assays in the presence of rat S-9 activation enzymes.

Travoprost did not affect mating or fertility indices in male or female rats at subcutaneous doses up to 10 *u*g/kg/day [250 times the maximum recommended human ocular dose of 0.04 *u*g/kg/day on a *u*g/kg basis (MRHOD)]. At 10 *u*g/kg/day, the mean number of corpora lutea was reduced, and the post-implantation losses were increased. These effects were not observed at 3 *u*g/kg/day (75 times the MRHOD).

Pregnancy: Teratogenic Effects

Pregnancy Category: C
Travoprost was teratogenic in rats, at an intravenous (IV) dose up to 10 *u*g/kg/day (250 times the MRHOD), evidenced by an increase in the incidence of skeletal malformations as well as external and visceral malformations, such as fused sternebrae, domed head and hydrocephaly. Travoprost was not teratogenic in rats at IV doses up to 3 *u*g/kg/day (75 times the MRHOD), and in mice at subcutaneous

doses up to 1.0 *u*g/kg/day (25 times the MRHOD). Travoprost produced an increase in post-implantation losses and a decrease in fetal viability in rats at IV doses > 3 *u*g/kg/day (75 times the MRHOD) and in mice at subcutaneous doses > 0.3 *u*g/kg/day (7.5 times the MRHOD).

In the offspring of female rats that received travoprost subcutaneously from Day 7 of pregnancy to lactation Day 21 at the doses of ≥ 0.12 *u*g/kg/day (3 times the MRHOD), the incidence of postnatal mortality was increased, and neonatal body weight gain was decreased. Neonatal development was also affected, evidenced by delayed eye opening, pinna detachment and preputial separation, and by decreased motor activity.

There are no adequate and well-controlled studies in pregnant women. TRAVATAN® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

A study in lactating rats demonstrated that radiolabeled travoprost and/or its metabolites were excreted in milk. It is not known whether this drug or its metabolites are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when TRAVATAN® is administered to a nursing woman.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

No overall differences in safety or effectiveness have been observed between elderly and other adult patients.

ADVERSE REACTIONS

The most common ocular adverse event observed in controlled clinical studies with TRAVATAN® 0.004% was ocular hyperemia which was reported in 35 to 50% of patients. Approximately 3% of patients discontinued therapy due to conjunctival hyperemia.

Ocular adverse events reported at an incidence of 5 to 10% included decreased visual acuity, eye discomfort, foreign body sensation, pain, and pruritus.

Ocular adverse events reported at an incidence of 1 to 4% included, abnormal vision, blepharitis, blurred vision, cataract, cells, conjunctivitis, dry eye, eye disorder, flare, iris discoloration, keratitis, lid margin crusting, photophobia, subconjunctival hemorrhage, and tearing.

Nonocular adverse events reported at a rate of 1 to 5% were accidental injury, angina pectoris, anxiety, arthritis, back pain, bradycardia, bronchitis, chest pain, cold syndrome, depression, dyspepsia, gastrointestinal disorder, headache, hypercholesterolemia, hypertension, hypotension, infection, pain, prostate disorder, sinusitis, urinary incontinence, and urinary tract infection.

DOSAGE AND ADMINISTRATION

The recommended dosage is one drop in the affected eye(s) once-daily in the evening. The dosage of TRAVATAN® should not exceed once-daily since it has been shown that more frequent administration may decrease the intraocular pressure lowering effect.

Reduction of intraocular pressure starts approximately 2 hours after administration, and the maximum effect is reached after 12 hours.

TRAVATAN® may be used concomitantly with other topical ophthalmic drug products to lower intraocular pressure. If more than one topical ophthalmic drug is being used, the drugs should be administered at least five (5) minutes apart.

HOW SUPPLIED

TRAVATAN® (travoprost ophthalmic solution) 0.004% is a sterile, isotonic, buffered, preserved, aqueous solution of travoprost (0.04 mg/mL) supplied in Alcon's oval DROP-TAINER® package system.

TRAVATAN® is supplied as a 2.5 mL solution in a 4 mL and a 5 mL solution in a 7.5 mL natural polypropylene dispenser bottle with a natural polypropylene dropper tip and a turquoise polypropylene overcap. Tamper evidence is provided with a shrink band around the closure and neck area of the package.

NDC 0065-0266-25, 2.5 mL fill
NDC 0065-0266-17, 2 units, 2.5 mL fill each
NDC 0065-0266-34, 5 mL fill

Storage
Store at 2° - 25°C (36° - 77°F).

Rx Only

U.S. Patent Nos. 5,631,287; 5,849,792; 5,889,052; 6,011,062, and 6,235,781.

*TIMOPTIC is a registered trademark of Merck & Co., Inc.

ALCON LOGO
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