

BAUSCH + LOMB

Travoflo™
(Travoprost Eye Drops IP 0.004% w/v)

GENERIC NAME

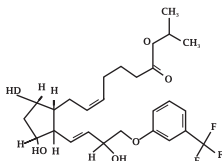
Travoprost Eye Drops IP 0.004% w/v

DOSAGE FORM

Ophthalmic Solution

DESCRIPTION

Travoprost is a synthetic prostaglandin F analogue. Its chemical name is [1R-[1 α (Z),2 β (1E,3R*),3 α ,5 α]]-7-[3,5Dihydroxy-2-[3-hydroxy-4-[3(trifluoromethyl)phenoxy]-1-butenyl]cyclopentyl]-5heptenoic acid, 1-methylethylester. It has a molecular formula of C₂₆H₃₅F₃O₆ and a molecular weight of 500.55. 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. Travoflo™ (Travoprost Eye Drops IP 0.004% w/v) is supplied as a sterile, buffered aqueous solution of travoprost with a pH of approximately 5.7 and an osmolality of approximately 290 mOsmol/kg.

COMPOSITION

Active: Travoprost IP 0.004% w/v

Inactive Ingredients: Zinc chloride, Polyoxyl 40 Hydrogenated Castor Oil, Boric acid, Propylene glycol, Neosorb 70/20, Sodium hydroxide, Hydrochloride acid

INDICATIONS

Travoflo™ ophthalmic solution is indicated for the reduction of intraocular pressure in patients with chronic open angle glaucoma or ocular hypertension

DOSAGE AND ADMINISTRATION

The recommended dosage is one drop in the affected eye(s) once daily in the evening. Travoflo™ 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. Reduction of the intraocular pressure starts approximately 2 hours after the first administration with maximum effect reached after 12 hours. Travoflo™ 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.

USE IN SPECIAL POPULATIONS

Pregnancy:

Category C: Teratogenic effects: There are no adequate and well-controlled studies of Travoprost Eye Drops 0.004% w/v administration in pregnant women. However as per the literature available, travoprost was found to be teratogenic in rats, at an intravenous (IV) dose up to 10 mcg/kg/day (250 times the maximal recommended human ocular dose (MRHOD), evidenced by an increase in the incidence of skeletal malformations as well as external and visceral malformations, such as fused sternbrae, domed head and hydrocephaly. Travoprost was not found to be teratogenic in rats at IV doses up to 3 mcg/kg/day (75 times the MRHOD), or in mice at subcutaneous doses up to 1 mcg/kg/day (25 times the MRHOD). Travoprost has been reported to produce an increase in post-implantation losses and a decrease in foetal viability in rats at IV doses >3 mcg/kg/day (75 times the MRHOD) and in mice at subcutaneous doses >0.3 mcg/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 doses of ≥ 0.12 mcg/kg/day (3 times the MRHOD), the reported 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. Because animal reproductive studies are not always predictive of human response, Travoprost Eye Drops 0.004% w/v should administered during pregnancy only if the potential benefit justifies the potential risk to the foetus.

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 Travoprost Eye Drops 0.004% w/v is administered to a nursing woman.

Pediatric Use

Use in pediatric patients below the age of 16 years is not recommended because of potential safety concerns related to increased pigmentation following long-term chronic use.

Geriatric Use

No overall clinical differences in safety or effectiveness have been reported between elderly and other adult patients. Hepatic and Renal Impairment Travoprost 0.004% w/v has been studied in patients with hepatic impairment and also in patients with renal impairment. No clinically relevant changes in hematology, blood chemistry, or urinalysis laboratory data were observed in these patients.

CONTRAINDICATIONS

Travoflo™ (Travoprost Eye Drops IP 0.004% w/v) is contraindicated in patients with known hypersensitivity to any ingredient in the formulation.

WARNINGS AND PRECAUTIONS

FOR EXTERNAL USE ONLY. NOT FOR INJECTION

Travoprost Eye Drops 0.004% w/v has been reported to cause changes to pigmented tissues. The most frequently reported changes have been increased pigmentation of the iris, periorbital tissue (eyelid) and eyelashes. Pigmentation is expected to increase as long as travoprost is





administered. The pigmentation change is due to increased melanin content in the melanocytes rather than to an increase in the number of melanocytes. After discontinuation of travoprost, pigmentation of the iris is likely to be permanent, while pigmentation of the periorbital tissue and eyelash changes have been reported to be reversible in some patients. Patients who receive treatment should be informed of the possibility of increased pigmentation. The long term effects of increased pigmentation are not known. Iris color change may not be noticeable for several months to years. Typically, the brown pigmentation around the pupil spreads concentrically towards the periphery of the iris and the entire iris or parts of the iris become more brownish. Neither nevi nor freckles of the iris appear to be affected by treatment. While treatment with Travoprost Eye Drops 0.004% w/v can be continued in patients who develop noticeably increased iris pigmentation, these patients should be examined regularly.

Eyelash Changes

Travoprost Eye Drops 0.004% w/v may gradually change eyelashes and vellus hair in the treated eye. These changes include increased length, thickness, and number of lashes. Eyelash changes are usually reversible upon discontinuation of treatment.

Intraocular Inflammation

Travoprost Eye Drops 0.004% w/v should be used with caution in patients with active intraocular inflammation (e.g., uveitis) because the inflammation may be exacerbated.

Macular Edema

Macular edema, including cystoid macular edema, has been reported during treatment with travoprost ophthalmic solution. Travoprost Eye Drops 0.004% w/v should be used with caution in aphakic patients, in pseudophakic patients with a torn posterior lens capsule, or in patients with known risk factors for macular edema.

Angle-closure, Inflammatory or Neovascular Glaucoma

Travoprost Eye Drops 0.004% w/v has not been reported for the treatment of angle-closure, inflammatory or neovascular glaucoma.

Bacterial Keratitis

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 ocular epithelial surface

DRUG INTERACTIONS

If more than one topical ophthalmic drug is being used, the drugs should be administered at least five (5) minutes before or after the other drug. Contact lenses should be removed prior to instillation of Travoflo™ and may be reinserted 15 minutes following its administration.

UNDESIRABLE EFFECTS

The data of controlled clinical studies with Travoprost Eye Drops 0.004% w/v indicates ocular hyperemia as the most common adverse reaction, which was reported in 30 to 50% of patients. Up to 3% of patients discontinued therapy due to conjunctival hyperemia. Ocular adverse reactions reported at an incidence of 5 to 10% in these clinical studies included decreased visual acuity, eye discomfort, foreign body sensation, pain and pruritus. Ocular adverse reactions reported at an incidence of 1 to 4% in clinical studies with Travoprost Eye Drops 0.004% w/v included

abnormal vision, blepharitis, blurred vision, cataract, conjunctivitis, corneal staining, dry eye, iris discoloration, keratitis, lid margin crusting, ocular inflammation, photophobia, subconjunctival hemorrhage and tearing. Non-ocular adverse reactions reported at an incidence of 1 to 5% in these clinical studies were allergy, angina pectoris, anxiety, arthritis, back pain, bradycardia, bronchitis, chest pain, cold/flu syndrome, depression, dyspepsia, gastrointestinal disorder, headache, hypercholesterolemia, hypertension, hypotension, infection, pain, prostate disorder, sinusitis, urinary incontinence and urinary tract infections.

PHARMACODYNAMIC AND PHARMACOKINETIC PROPERTIES

Pharmacodynamics:

Mechanism of Action

Travoprost free acid, a prostaglandin analogue 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

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 C_{max} was 0.018 ± 0.007 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. 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 analogues, via oxidation of the 15-hydroxyl moiety, as well as via reduction of the 13,14 double bond. 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 mm Hg who were treated with Travoprost 0.004% w/v dosed once-daily in the evening demonstrated 7-8 mm Hg reductions in intraocular pressure. In subgroup analyses of these studies, mean IOP reduction in black patients was up to 1.8 mm Hg 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 mm Hg on TIMOLOL 0.5% BID who were treated with travoprost ophthalmic solution 0.004% dosed QD adjunctively to TIMOLOL 0.5% BID demonstrated 6-7 mm Hg reductions in intraocular pressure.



NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

Two-year carcinogenicity studies in mice and rats at subcutaneous doses of 10, 30, or 100 mcg/kg/day did not show any evidence of carcinogenic potential. However, at 100 mcg/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 mcg/kg) corresponds to exposure levels over 400 times the human exposure at the maximum recommended human ocular dose (MRHOD) of 0.04 mcg/kg, based on plasma active drug levels. Travoprost was not found to be mutagenic in the Ames test, mouse micronucleus test or 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 is not reported to affect mating or fertility indices in male or female rats at subcutaneous doses up to 10 mcg/kg/day [250 times the maximum recommended human ocular dose of 0.04 mcg/kg/day on a mcg/kg basis (MRHOD)]. At 10 mcg/kg/day, the mean number of corpora lutea was reduced, and the post-implantation losses were increased. These effects were not observed at 3 mcg/kg/day (75 times the MRHOD).

OVERDOSE

There is no experience of overdose by the ophthalmic route. Overdose is unlikely to occur via the recommended route of administration.

INFORMATION FOR PATIENTS

- Patients are advised that there is increased potential for brown pigmentation of the iris, which may be permanent. There is also the possibility of eyelid skin darkening, which may be reversible after discontinuation of Travoprost Eye Drops 0.004% w/v application.
- There is a possibility of eyelash and vellus hair changes in the treated eye during treatment with Travoprost Eye Drops 0.004% w/v. Eyelash changes are usually reversible upon discontinuation of treatment.
- Travoflo™ is sterile when packed. Patients must not allow the dropper tip/ dispensing tip to touch any surface, as this may contaminate the solution.
- If trauma or infection, particularly conjunctivitis and eyelid reactions are seen, patient should immediately seek their physician's advice concerning the continued use of Travoflo™.
- It is advised to remove contact lenses prior to instillation of Travoflo™ and may be reinserted 15 minutes following its administration
- If more than one topical ophthalmic drug is being used, the drugs should be administered at least five (5) minutes between applications.
- Use the solution within one month of opening the container.

INCOMPATIBILITIES

Not reported

SHELF LIFE

Please see Mfg. Date/ Expiry Date printed on pack. Do not use the product after the expiry date which is stated on the packaging. The expiry date refers to the last day of that month.

PACKAGING INFORMATION

Travoflo™ (Travoprost Eye Drops IP 0.004% w/v) is supplied in a 3 ml plastic bottle with a white cap.

STORAGE AND HANDLING INSTRUCTIONS

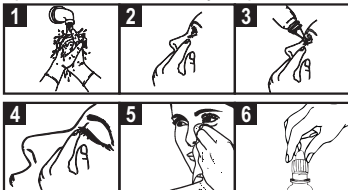
Store at a temperature not exceeding 30°C. Protect from light. Use the solution within one month after opening the container.

KEEP ALL MEDICINES OUT OF REACH OF CHILDREN

REFERENCES:

US Prescribing information of TRAVATAN Z®, Alcon®, Alcon Laboratories, Inc. Fort Worth, Texas 76134 USA. Information compiled in December 2011

Tips for Safe Administration of Eye Drops[†]



1. Wash your hands thoroughly before administration.
2. Bend your head backwards and gently pull your lower eyelid down.
3. Turn the bottle upside down and squeeze it to release one drop into each eye that needs treatment.
4. Let go of the lower lid, and close your eye for 30 seconds.
5. Wipe away any liquid that falls onto your cheek with a tissue.
6. Close the cap immediately after use.

Take Care of your eye drops:

- Do not let the dropper or dispensing tips touch your eye, finger, or any other surface.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If more than one type of Eye Drops are used, wait for at least five minutes before administering the second medication to avoid washout of the previous drug.
- Consult your physician if eye symptoms become worse after using eye drops.

[†]Read this entire leaflet carefully before you start using this medicine.

Keep this leaflet. You may need to read it again. If you have any further questions, ask your Physician.

Marketed by:

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