

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use TRAVOPROST OPHTHALMIC SOLUTION (IONIC BUFFERED SOLUTION) 0.004% safely and effectively. See full prescribing information for TRAVOPROST OPHTHALMIC SOLUTION (IONIC BUFFERED SOLUTION) 0.004%.

TRAVOPROST ophthalmic solution (ionic buffered solution) 0.004%, for topical ophthalmic use

Initial U.S. Approval: 2001

-----INDICATIONS AND USAGE-----

Travoprost ophthalmic solution (ionic buffered solution) 0.004% is a prostaglandin analog indicated for the reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension. (1)

-----DOSAGE AND ADMINISTRATION-----

One drop in the affected eye(s) once daily in the evening. (2)

-----DOSAGE FORMS AND STRENGTHS-----

Ophthalmic solution containing travoprost 0.04 mg/mL (3)

-----CONTRAINDICATIONS-----

None (4)

-----WARNINGS AND PRECAUTIONS-----

- Pigmentation.
Pigmentation of the iris, periorbital tissue (eyelid) and eyelashes can occur. Iris pigmentation likely to be permanent. (5.1)
- Eyelash Changes.
Gradual change to eyelashes including increased length, thickness and number of lashes. Usually reversible. (5.2)

-----ADVERSE REACTIONS-----

Most common adverse reaction (30% to 50%) is conjunctival hyperemia. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Apotex Corp. at 1-800-706-5575 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

-----USE IN SPECIFIC POPULATIONS-----

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. (8.4)

See 17 for PATIENT COUNSELING INFORMATION

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Travoprost ophthalmic solution (ionic buffered solution) 0.004% is indicated for the reduction of elevated intraocular pressure in patients with open angle glaucoma or ocular hypertension.

2 DOSAGE AND ADMINISTRATION

The recommended dosage is one drop in the affected eye(s) once daily in the evening. Travoprost ophthalmic solution (ionic buffered solution) should not be administered more than once daily since it has been shown that more frequent administration of prostaglandin analogs 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.

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

3 DOSAGE FORMS AND STRENGTHS

Ophthalmic solution containing travoprost 0.04 mg/mL.

4 CONTRAINDICATIONS

None

5 WARNINGS AND PRECAUTIONS

5.1 Pigmentation

Travoprost ophthalmic solution 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 ophthalmic solution (ionic buffered solution) 0.004% can be continued in patients who develop noticeably increased iris pigmentation, these patients should be examined regularly [see PATIENT COUNSELING INFORMATION (17)].

5.2 Eyelash Changes

Travoprost ophthalmic solution (ionic buffered solution) 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.

5.3 Intraocular Inflammation

Travoprost ophthalmic solution (ionic buffered solution) should be used with caution in patients with active intraocular inflammation (e.g., uveitis) because the inflammation may be exacerbated.

5.4 Macular Edema

Macular edema, including cystoid macular edema, has been reported during treatment with travoprost ophthalmic solution. Travoprost ophthalmic solution (ionic buffered solution) 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.

5.5 Angle-closure, Inflammatory or Neovascular Glaucoma

Travoprost ophthalmic solution (ionic buffered solution) has not been evaluated for the treatment of angle-closure, inflammatory or neovascular glaucoma.

5.6 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 [see *PATIENT COUNSELING INFORMATION* ([17](#))].

5.7 Use with Contact Lenses

Contact lenses should be removed prior to instillation of travoprost ophthalmic solution (ionic buffered solution) and may be reinserted 15 minutes following its administration.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The most common adverse reaction observed in controlled clinical trials with travoprost ophthalmic solution 0.004% and travoprost ophthalmic solution (ionic buffered solution) 0.004% was ocular hyperemia 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 trials 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 trials with travoprost ophthalmic solution or travoprost ophthalmic solution (ionic buffered solution) 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.

Nonocular 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.

6.2 Postmarketing Experience

Additional adverse reactions have been identified during post approval use of travoprost ophthalmic solution or travoprost ophthalmic solution (ionic buffered solution) in clinical practice. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. The reactions, which have been chosen for inclusion due to either their seriousness, frequency of reporting, possible causal connection to travoprost ophthalmic solution or travoprost ophthalmic solution (ionic buffered solution), or a combination of these factors, include: arrhythmia, vomiting, epistaxis, tachycardia, and insomnia.

In postmarketing use with prostaglandin analogs, periorbital and lid changes including deepening of the eyelid sulcus have been observed.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

Teratogenic effects: Travoprost was teratogenic in rats, at an intravenous 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 sternebrae, domed head and hydrocephaly. Travoprost was not teratogenic in rats at intravenous 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 produced an increase in post-implantation losses and a decrease in fetal viability in rats at intravenous doses greater than 3 mcg/kg/day (75 times the MRHOD) and in mice at subcutaneous doses greater than 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 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 of travoprost ophthalmic solution (ionic buffered solution) 0.004% administration in pregnant women. Because animal reproductive studies are not always predictive of human response, travoprost ophthalmic solution (ionic buffered solution) should be administered during pregnancy only if the potential benefit justifies the potential risk to the fetus.

8.3 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 ophthalmic solution (ionic buffered solution) is administered to a nursing woman.

8.4 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.

8.5 Geriatric Use

No overall clinical differences in safety or effectiveness have been observed between elderly and

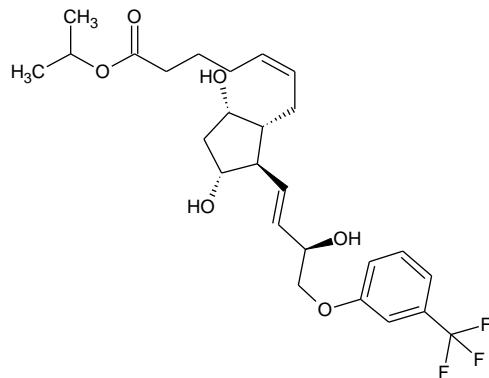
other adult patients.

8.6 Hepatic and Renal Impairment

Travoprost ophthalmic solution 0.004% 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.

11 DESCRIPTION

Travoprost is a synthetic prostaglandin F analogue. Its chemical name is [1*R*-[1*a*(*Z*),2*β*(1*E*,3*R*^{*}),3*a*,5*a*]-7-[3,5-Dihydroxy-2-[3-hydroxy-4-[3-(trifluoromethyl) phenoxy]-1-butene]cyclopentyl]-5-heptenoic acid, 1-methylethylester. It has a molecular formula of C₂₆H₃₅F₃O₆ and a molecular weight of 500.55 g/mol. 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.

Travoprost ophthalmic solution, USP (ionic buffered solution) 0.004% is supplied as sterile, buffered aqueous solution of travoprost with a pH of approximately 5.7 and an osmolality of approximately 290 mOsmol/kg.

Travoprost ophthalmic solution, USP (ionic buffered solution) contains **Active**: travoprost 0.04 mg/mL; **Inactives**: polyoxyxyl 40 hydrogenated castor oil, ionic buffered system (boric acid, propylene glycol, sorbitol, zinc chloride), sodium hydroxide and/or hydrochloric acid (to adjust pH) and water for injection. Preserved in the bottle with an ionic buffered system.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Travoprost free acid, a prostaglandin analog 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.

12.3 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 analogs, 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.

13 NONCLINICAL TOXICOLOGY

13.1 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 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 did not affect mating or fertility indices in male or female rats at subcutaneous doses up to 10 mcg/kg/day [250 times the MRHOD of 0.04 mcg/kg/day on a mcg/kg basis]. 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).

14 CLINICAL STUDIES

In clinical studies, patients with open-angle glaucoma or ocular hypertension and baseline pressure of 25 to 27 mmHg who were treated with travoprost ophthalmic solution 0.004% or travoprost ophthalmic solution (ionic buffered solution) 0.004% dosed once-daily in the evening demonstrated 7 to 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 to 26 mmHg on TIMOPTIC* 0.5% twice daily who were treated with travoprost ophthalmic solution 0.004% dosed daily adjunctively to TIMOPTIC* 0.5% twice daily demonstrated 6 to 7 mmHg reductions in intraocular pressure.

16 HOW SUPPLIED/STORAGE AND HANDLING

Travoprost ophthalmic solution, USP (ionic buffered solution) 0.004% is a sterile, isotonic, buffered,

preserved, aqueous solution of travoprost (0.04 mg/mL).

Travoprost ophthalmic solution, USP (ionic buffered solution) 0.004% is supplied as a 2.5 mL solution and a 5 mL solution in a 5 mL translucent polypropylene ophthalmic bottle with a translucent polypropylene ophthalmic dropper and a turquoise, opaque polypropylene cap.

2.5 mL fill NDC 60505-0593-4
5 mL fill NDC 60505-0593-1

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

17 PATIENT COUNSELING INFORMATION

Potential for Pigmentation

Advise the patient about the potential for increased brown pigmentation of the iris, which may be permanent. Inform the patient about the possibility of eyelid skin darkening, which may be reversible after discontinuation of travoprost ophthalmic solution (ionic buffered solution) 0.004%.

Potential for Eyelash Changes

Inform the patient about the possibility of eyelash and vellus hair changes in the treated eye during treatment with travoprost ophthalmic solution (ionic buffered solution). These changes may result in a disparity between eyes in length, thickness, pigmentation, number of eyelashes or vellus hairs, and/or direction of eyelash growth. Eyelash changes are usually reversible upon discontinuation of treatment.

Handling the Container

Instruct the patient to avoid allowing the tip of the dispensing container to contact the eye, surrounding structures, fingers, or any other surface in order to avoid contamination of the solution by common bacteria known to cause ocular infections. Serious damage to the eye and subsequent loss of vision may result from using contaminated solutions.

When to Seek Physician Advice

Advise the patient that if they develop an intercurrent ocular condition (e.g., trauma or infection), have ocular surgery, or develop any ocular reactions, particularly conjunctivitis and eyelid reactions, they should immediately seek their physician's advice concerning the continued use of travoprost ophthalmic solution (ionic buffered solution).

Use with Contact Lenses

Contact lenses should be removed prior to instillation of travoprost ophthalmic solution (ionic buffered solution) and may be reinserted 15 minutes following its administration.

Use with Other Ophthalmic Drugs

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

Rx Only

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

Manufactured by:

Manufactured for:

Apotex Inc.
Toronto, Ontario
Canada, M9L 1T9

Apotex Corp.
Weston, Florida
33326

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