

PRODUCT MONOGRAPH
INCLUDING PATIENT MEDICATION INFORMATION

Pr **SANDOZ TRAVOPROST**

Travoprost Ophthalmic Solution

0.004% w/v

Elevated Intraocular Pressure Therapy
Prostaglandin F_{2α} analogue

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Table of Contents

PART I: HEALTH PROFESSIONAL INFORMATION.....3
SUMMARY PRODUCT INFORMATION3
INDICATIONS AND CLINICAL USE.....3
CONTRAINDICATIONS3
WARNINGS AND PRECAUTIONS.....3
ADVERSE REACTIONS.....6
DRUG INTERACTIONS9
DOSAGE AND ADMINISTRATION9
OVERDOSAGE9
ACTION AND CLINICAL PHARMACOLOGY10
STORAGE AND STABILITY10
DOSAGE FORMS, COMPOSITION AND PACKAGING11

PART II: SCIENTIFIC INFORMATION12
PHARMACEUTICAL INFORMATION.....12
CLINICAL TRIALS12
DETAILED PHARMACOLOGY14
TOXICOLOGY18
REFERENCES20

PART III: PATIENT MEDICATION INFORMATION21

Pr **SANDOZ TRAVOPROST**
Travoprost Ophthalmic Solution

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Ophthalmic (topical)	Ophthalmic solution/ travoprost 0.004% w/v	sofZIA [®] preservative system. <i>For a complete listing see Dosage Forms, Composition and Packaging section.</i>

INDICATIONS AND CLINICAL USE

Sandoz Travoprost is indicated for the reduction of intraocular pressure in adult patients with open-angle glaucoma or ocular hypertension.

Pediatrics (< 18 years of age):

The safety and effectiveness of **Sandoz Travoprost** have not been established in pediatric patients, and its use is not recommended in these patients.

CONTRAINDICATIONS

Sandoz Travoprost is contraindicated in:

- Patients who are hypersensitive to travoprost or to any ingredient in the formulation or component of the container. For a complete listing, see DOSAGE FORMS, COMPOSITION AND PACKAGING.

Sandoz Travoprost may interfere with the maintenance of pregnancy and should not be used by women during pregnancy or by women attempting to become pregnant.

WARNINGS AND PRECAUTIONS

General

FOR OPHTHALMIC USE ONLY.

Sandoz Travoprost is a benzalkonium chloride-free formulation of travoprost ophthalmic solution. In phase III clinical trials, travoprost ophthalmic solution containing BAC was studied

adjunctively with TIMOPTIC*. No additional adjunctive studies have been done.

If signs and symptoms of hypersensitivity develop, in particular conjunctivitis and lid reactions, patients should be advised to immediately seek their physician's advice.

Driving and Using Machinery: Temporary blurred vision or other visual disturbances may affect the ability to drive or use machines. If blurred vision occurs after application of **Sandoz Travoprost**, the patient must wait until vision clears before driving or using machinery.

Hepatic/Renal

Travoprost ophthalmic solution containing BAC has been studied in patients with mild to severe hepatic impairment (Childs-Pugh Classification A - C) and also in patients with mild to severe renal impairment (creatinine clearance from as low as 14 mL/min/1.73 m² to 77 mL/min/1.73 m²)¹. No clinically relevant changes in hematology, blood chemistry, urinalysis laboratory data or plasma concentrations of free acid were observed in patients with impaired (mild, moderate, or severe) hepatic or renal function. No dosage adjustment is necessary in patients with hepatic or renal impairment.

Ophthalmologic

There is no experience of **travoprost** in inflammatory ocular conditions; nor in neovascular or angle-closure glaucoma.

Sandoz Travoprost should be used with caution in patients with active intraocular inflammation (iritis/uveitis).

Patients should remove contact lenses prior to administration of **Sandoz Travoprost**. Lenses may be reinserted 15 minutes following administration of **Sandoz Travoprost**.

Macular edema: Macular edema, including cystoid macular edema, has been reported during treatment with prostaglandin F_{2α} 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. **Sandoz Travoprost** should be used with caution in these patients.

Multi-dose container: 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.

Patients should 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 inter-current ocular condition (e.g., trauma, or infection) or have ocular surgery, they should immediately seek their physician's

¹ Sandoz Travoprost is a benzalkonium chloride-free formulation of travoprost ophthalmic solution containing BAC.

advice concerning the continued use of the multi-dose container.

Ocular Effects: Travoprost 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 any consequences of potential injury to the melanocytes and/or deposition of pigment granules to other areas of the eye are currently unknown. 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. The change in iris color occurs slowly and may not be noticeable for months to years. In clinical trials, iris pigmentation was detected as early as 3 months. This change in eye color has predominantly been seen 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. These changes may be permanent. Patients should be informed of the possibility of iris color change. There are no clinical data on treatment with travoprost ophthalmic solution containing BAC beyond five years².

Periorbital and/or eyelid skin darkening has been reported in association with the use of travoprost.

Periorbital and lid changes, including deepening of the eyelid sulcus have been observed with prostaglandin analogues.

Travoprost may gradually change eyelashes in the treated eye; these changes include: increased length, thickness, pigmentation, and/or number of lashes. During long-term clinical trials, eyelash photographs taken periodically during the studies, revealed an overall incidence of eyelash changes of 61%. The overall incidence of patient complaints regarding these changes was 0.8%. Changes in eyelashes may be noticed as early as one and a half months after initiation of treatment. The mechanism of eyelash changes and their long term consequence are currently unknown.

Patients who receive treatment in only one eye may experience increased brown pigmentation of the iris, periorbital and/or eyelid tissue, and eyelashes in the treated eye. They may also experience disparity between the eyes in length, thickness, and/or number of eyelashes. These changes in pigmentation and lash growth may be permanent.

Special Populations

Women of Childbearing Age and Pregnant Women: No adequate and well-controlled studies have been performed in pregnant women. Travoprost, like all FP agonists, may interfere with the maintenance of pregnancy and should not be used by women during pregnancy or by women attempting to become pregnant.

Travoprost was teratogenic in rats. Travoprost administered intravenously to pregnant rats from gestation Days 6-17 at a dose of 10 mcg/kg/day, induced a slight increase in the incidence of skeletal malformations such as fused sternbrae, domed head and hydrocephaly. No effect was observed at 3 mcg/kg/day (75 times the maximum recommended human dose of 0.04

² Sandoz Travoprost is a benzalkonium chloride-free formulation of travoprost ophthalmic solution containing BAC.

mcg/kg/day). The no effect level for fetal external, visceral or skeletal malformation was observed after 1.0 mcg/kg/day subcutaneous administration during gestation days 6-16 to pregnant mice, though post-implantation loss was increased at that dose, but not at 0.3 mcg/kg/day.

Since prostaglandins are biologically active and 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 with soap and water immediately.

Nursing Women: 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 **Sandoz Travoprost** is administered to a nursing woman.

Pediatrics (< 18 years of age): Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Sandoz Travoprost is a benzalkonium chloride-free formulation of travoprost ophthalmic solution containing BAC . Ocular hyperemia was reported in 40% of all patients receiving travoprost ophthalmic solution containing BAC and **travoprost**. Approximately 80 to 90% of the ocular hyperemia was mild in intensity and subsided over time without treatment. Up to three percent of the patients discontinued therapy due to conjunctival hyperemia. Table 1 summarizes adverse reactions reported with travoprost ophthalmic solution containing BAC.

During clinical studies, there were extremely rare reports of the following: choroidal nevus, retinal detachment, retinal hemorrhage, retinal pigmentation, and vitreous detachment.

Table 1: Overall (Related & Unrelated) Frequency and Incidence of Adverse Events Occurring at an Incidence \geq 1.0%

	Travoprost ophthalmic solution 0.004% containing BAC (n=656)		Travoprost ophthalmic solution 0.004% containing BAC + Timolol 0.5% (n=145)	
	n	%	n	%
Ocular				
Hyperemia eye	259	39.5	52	35.9
Discomfort eye	35	5.3	7	4.8

Pruritus eye	48	7.3	5	3.4
Visual acuity decrease	29	4.4	6	4.1
Iris discoloration ³	15	2.3	0	-
Dry eye	20	3.0	8	5.5
Foreign body sensation	24	3.7	4	2.8
Pain eye	33	5.0	6	4.1
Keratitis	17	2.6	3	2.1
Vision blurred	13	2.0	3	2.1
Cataract NOS	13	2.0	1	0.7
Blepharitis	11	1.7	2	1.4
Cells	7	1.1	6	4.1
Hemorrhage subconjunctival	7	1.1	0	-
Conjunctivitis	10	1.5	2	1.4
Flare	7	1.1	2	1.4
Photophobia	8	1.2	4	2.8
Tearing	7	1.1	3	2.1
Lid disorder	1 ⁴	0.2	3 ⁵	2.1
Eye fatigue	2	0.3	2	1.4
Sticky sensation	1	0.2	2	1.4
Non-ocular				
<u>Body as a Whole</u>				
Surgical/Medical Procedure	31	4.7	4	2.8
Infection	24	3.7	3	2.1
Headache	20	3.0	2	1.4
Pain	14	2.1	0	-
Injury accidental	17	2.6	1	0.7
Cold syndrome	10	1.5	3	2.1
Flu syndrome	17	2.6	2	1.4
Allergy	3	0.5	2	1.4
<u>Cardiovascular System</u>				
Hypertension	27	4.1	2	1.4
<u>Digestive System</u>				
GI disorder	10	1.5	1	0.7
<u>Metabolic and Nutritional</u>				
Hypercholesteremia	11	1.7	0	-
<u>Nervous System</u>				
Depression	9	1.4	2	1.4
<u>Respiratory System</u>				
Sinusitis	11	1.7	3	2.1
Bronchitis	7	1.1	1	0.7
Rhinitis	7	1.1	1	0.7
<u>Urogenital System</u>				
Infection urinary tract	7	1.1	3	2.1
Prostate disorder	6	0.9	2	1.4

A similar safety profile was observed in a clinical trial of three months duration, comparing therapy with **Sandoz Travoprost** (399 patients dosed QD in the evening) to travoprost

³ Increases in brown pigmentation of the iris

⁴ Lid pigment (1)

⁵ Prominent vessel (1), sore spot (1), lid lesion (1)

ophthalmic solution containing BAC (400 patients dosed QD in the evening).⁶

Post-Market Adverse Drug Reactions

The following serious, unexpected reactions reported during the post-market use of travoprost ophthalmic solution containing BAC in clinical practice and in the literature have been included based on the frequency of reporting, possible causal connection to travoprost ophthalmic solution containing BAC, or a combination of these factors:

Eye Disorders: corneal edema, macular edema;

Cardiac disorders: bradycardia, tachycardia;

General disorders and administration site conditions: chest discomfort;

Respiratory, thoracic and mediastinal disorders: asthma, dyspnea.

Additional adverse drug reactions reported in subsequent clinical trials with travoprost and travoprost ophthalmic solution containing BAC include the following:

Cardiac disorders: heart rate decreased, palpitations;

Eye disorders: anterior chamber inflammation, anterior chamber pigmentation, asthenopia, conjunctival edema, conjunctival follicles, corneal erosion, eczema eyelids, erythema of eyelid, eye allergy, eye discharge, eye inflammation, eyelash hyperpigmentation, eyelash thickening, eyelid irritation, eyelid margin crusting, eyelid pruritis, growth of eyelashes, hypoaesthesia eye, iridocyclitis, ophthalmic herpes simplex, periorbital edema, punctate keratitis, trichiasis;

Gastrointestinal disorders: constipation, dry mouth;

General disorders and administration site conditions: asthenia;

Musculoskeletal and connective tissue disorders: arthralgia, musculoskeletal pain;

Nervous system disorders: dizziness, dysgeusia;

Respiratory, thoracic and mediastinal disorders: cough, dysphonia, nasal discomfort, nasal dryness, oropharyngeal pain;

Skin and subcutaneous tissue disorders: erythema, hair colour changes, hypertrichosis, madarosis, rash, skin discolouration, skin hyperpigmentation;

Vascular disorders: hypotension.

Adverse reactions identified from post-marketing surveillance include the following:

Cardiac disorders: arrhythmia, tachycardia;

Ear and labyrinth disorders: tinnitus;

Eye disorders: sunken eyes;

Gastrointestinal disorders: abdominal pain, diarrhea, nausea, vomiting;

Investigations: prostate specific antigen increased;

Psychiatric disorders: anxiety, insomnia;

Renal and urinary disorders: dysuria, urinary incontinence;

Respiratory, thoracic and mediastinal disorders: epistaxis;

Skin and subcutaneous tissue disorders: pruritis.

A few case reports of iritis/uveitis associated with the use of travoprost have been published. These cases occurred a few days after travoprost use in patients without a history of iritis/uveitis.

⁶ Sandoz Travoprost is a benzalkonium chloride-free formulation of travoprost ophthalmic solution containing BAC.

All of these cases resolved after stopping travoprost with or without corticosteroid treatment.

DRUG INTERACTIONS

Drug interaction studies have not been performed with travoprost. Drug-drug, drug-food, drug-herb, drug-laboratory, and drug-lifestyle interactions have not been established.

DOSAGE AND ADMINISTRATION

Recommended Dose

The recommended dosage is one drop in the affected eye(s) once-daily. Optimal effect is observed with evening dosing. The dosage of **Sandoz Travoprost** 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.

Administration

Sandoz Travoprost may be used concomitantly with topical ophthalmic beta-blockers 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.

To avoid contamination, patients should be instructed to avoid allowing the dispenser tip to touch the eye or surrounding areas. Serious damage to the eye and subsequent loss of vision may result from using contamination solutions.

Missed dose

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.

OVERDOSAGE

A single-dose intravenous study in rats was conducted to elucidate maximal acute hazard. The dose employed was 250,000-times the proposed daily clinical exposure and over 5000-times the possible exposure from the entire contents of one product container. No treatment related pharmacotoxic signs were present in the animals receiving travoprost.

If overdosage with **Sandoz Travoprost** occurs, treatment should be symptomatic.

For management of a suspected drug overdose, including oral ingestion, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Travoprost, an isopropyl ester prodrug, is rapidly hydrolyzed by esterases in the cornea to the biologically active free acid. Travoprost free acid is a highly selective, potent agonist for the FP prostanoid receptor. FP receptor agonists are thought to reduce intraocular pressure (IOP) by increasing the outflow of aqueous humor, primarily by increased uveoscleral outflow.

Pharmacodynamics

Travoprost, when applied topically to the eye, reduces elevated as well as normal IOP, whether or not accompanied by glaucoma. Elevated IOP is a major risk factor in the pathogenesis of glaucomatous visual field loss. The higher the level of IOP, the greater the likelihood of glaucomatous visual field loss and optic nerve damage. The Advanced Glaucoma Intervention Study (AGIS) (1) established elevated IOP as a positive risk factor for glaucomatous visual field loss. Eyes with intraocular pressures below 18 mmHg at all visits were found to have little to no visual field loss during the six-year monitoring period.

Pharmacokinetics

Absorption: Travoprost is absorbed through the cornea. Studies in rabbits have shown peak concentrations in aqueous humor were reached one to two hours following topical administration. In humans, peak plasma concentrations of travoprost free acid were low (25 pg/mL or less) and occurred within 30 minutes following topical ocular administration of one drop of 0.004% travoprost ophthalmic solution.

Distribution: Travoprost free acid is moderately distributed into body tissues with a volume of distribution of 2.6 L/kg in rats. Radioactivity levels in rat tissues following a single subcutaneous dose of ¹⁴C-travoprost dropped rapidly during the first 3 hours and by 24 hours were below or near detection limits (<0.2 - 6 ng equiv./g). Binding of travoprost free acid to plasma proteins is moderate at 80% and linear over a 10,000-fold concentration range (0.10 - 100 ng/mL).

Metabolism: Metabolism was studied in rats, dogs and monkeys. Systemically, travoprost free acid is rapidly and extensively metabolized in the kidney, liver and lung to inactive metabolites. Biotransformations include beta-oxidation of the α (carboxylic acid) chain to give the 1, 2-dinor and 1, 2, 3, 4-tetranor analogs, oxidation of the 15-hydroxyl moiety, as well as reduction of the 13, 14 double bond.

Excretion: In rats, 95% of a subcutaneous radiolabeled dose was eliminated within 24 hours. The major route of elimination was via the bile (61%) with the remainder excreted by the kidneys. In humans, elimination from plasma was rapid resulting in concentrations below the limit of quantitation (< 10 pg/mL) by one hour.

STORAGE AND STABILITY

Store between 2°C to 25°C. Keep out of the reach and sight of children.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Sandoz Travoprost 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.

Each mL of **Sandoz Travoprost** contains:

Medicinal ingredient: 40 mcg travoprost.

Non-medicinal ingredients: polyoxyl 40 hydrogenated castor oil, purified water, sofZia preservative system (boric acid, propylene glycol, sorbitol, zinc chloride), and sodium hydroxide and/or hydrochloric acid (to adjust pH).

Preserved in the bottle with an ionic buffered system, sofZia.

Sandoz Travoprost is supplied in the oval DROP-TAINER[®] dispenser bottle. This plastic oval-shaped dispenser bottle, containing 2.5mL or 5mL, includes a tamper-evident neck-band which shrinks to conform around the closure and neck area of the package.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

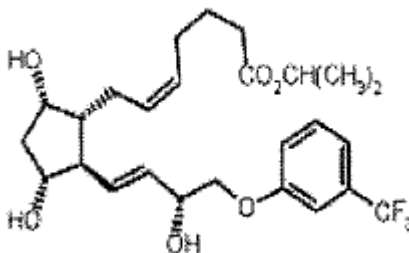
Drug Substance

Proper name: Travoprost

Chemical name: [1R-[1 α (Z),2 β (1E,3R*),3 α ,5 α]]-7-[3,5-Dihydroxy-2-[3-hydroxy-4-[3-(trifluoromethyl)phenoxy]-1-butenyl]cyclopentyl]-5-heptenoic acid, 1-methylethyl ester

Molecular formula and molecular mass: C₂₆H₃₅F₃O₆; 500.56

Structural formula:



Physicochemical properties: Travoprost is a clear, colorless to pale yellow oil; very soluble in acetonitrile, methanol, octanol, and chloroform; practically insoluble in water.

CLINICAL TRIALS

Sandoz Travoprost is a benzalkonium chloride-free formulation of travoprost Ophthalmic Solution. In three controlled clinical studies, with durations from 6 to 12 months, patients with open-angle glaucoma or ocular hypertension were treated once daily in the evening with travoprost ophthalmic solution, containing BAC. Travoprost ophthalmic solution containing BAC reduced IOP 6.7 to 9.0 mmHg. Stable diurnal IOP reductions were achieved as early as 2 weeks after initiation of therapy and were maintained over the 6 to 12 month treatment period.

In a multi-center, randomized, controlled trial, patients with mean baseline IOP of 24-26 mmHg on TIMOPTIC* 0.5% BID, who were treated with travoprost ophthalmic solution, 0.004% containing BAC dosed QD adjunctively to TIMOPTIC* 0.5% BID, demonstrated 6-7 mmHg additional reductions in IOP.

There are no plasma interactions with the concomitant administration of travoprost and timolol.

Summary of Patient Demographics for Clinical Trials in Specific Indication

Study #	Trial Design	Dosage, Route of Administration and Duration	Study Subjects	Mean age (range)	Gender
C-97-71	Randomised, triple masked, multicentre, parallel group, active control in patients with open-angle glaucoma or ocular hypertension	1 drop QD of placebo (8 AM) + 1 drop QD (8 PM) travoprost 0.004% or 0.0015%; 1 drop QD of placebo (8 AM) + 1 drop QD (8 PM) latanoprost 0.005%; or 1 drop BID of TIMOPTIC* 0.5% (8 AM and 8 PM); 12 months	787	64.2 years (22-94)	392 M 395 F
C-97-72	Randomised, triple masked, multicentre, parallel group, active control in patients with open-angle glaucoma or ocular hypertension	1 drop QD of placebo (8 AM) + 1 drop QD (8 PM) travoprost 0.004% or 0.0015%; or 1 drop of TIMOPTIC* 0.5% (8 AM and 8 PM); 6 months	594	63.7 years (21-91)	293 M 301 F
C-97-73	Randomised, multicentre, triple masked, vehicle-controlled, parallel group study in patients with open-angle glaucoma or ocular hypertension who were uncontrolled after a 3-week run-in on TIMOPTIC* 0.5% dosed BID	1 drop QD (8 PM) of travoprost 0.004% or 0.0015% plus 1 drop BID of open-label TIMOPTIC* 0.5% (8 AM and 8PM); or 1 drop WD (8 PM) of placebo plus 1 drop BID of open-label TIMOPTIC* 0.5% (8 AM and 8 PM); 6 months	410	63.7 years (11-89)	180 M 230 F
C-97-79	Randomised, multicentre, triple masked, active controlled, parallel group study in patients with open-angle glaucoma or ocular hypertension	1 drop QD of placebo (9 AM) + 1 drop QD (9 PM) travoprost 0.004% or 0.0015%; or 1 drop BID of TIMOPTIC* 0.5% (9 AM and 9 PM); 9 months	572	63.3 years (31-88)	284 M 288 F
C-01-74	Randomised, double-masked, multicentre, parallel group, active-controlled in patients with open-angle glaucoma or ocular hypertension	1 drop QD of placebo (9 AM) + 1 drop QD (9 PM) travoprost 0.004%; or 1 drop QD of latanoprost/timolol 0.5% (9 AM) + 1 drop QD of placebo (9 PM); 6 weeks	106	68.0 years (34-86)	46 M 60 F

Mean Baseline IOP and Mean Change from Baseline IOP Measurements

Study (Duration)	Baseline Mean IOP (mmHg)			Mean IOP Change from Baseline (mmHg)		
	8 AM	10 AM	4 PM	8 AM	10 AM	4 PM
C-97-71						
Travoprost ophthalmic solution containing BAC	26.8	25.2	24.6	-7.6	-7.4	-6.9
Timolol	26.9	25.3	24.6	-6.7 ^c	-6.1 ^c	-5.3 ^c
Latanoprost	26.9	25.2	24.9	-7.7	-6.9	-6.3 ^c
C-97-72						
Travoprost ophthalmic solution containing BAC	27.3	25.7	25.1	-7.6	-7.2	-7.0
Timolol	27.4	25.8	25.4	-6.8 ^c	-6.0 ^c	-5.1 ^c
C-97-73						
Travoprost ophthalmic solution containing BAC /Timolol	26.0	24.5	24.6	-6.8	-6.4	-6.0
Timolol	26.4	24.8	24.4	-2.6 ^c	-1.8 ^c	-1.6 ^c
C-97-79^a						
Travoprost ophthalmic solution containing BAC	27.4	26.5	25.6	-8.8	-8.7	-8.2
Timolol	27.0	26.2	25.1	-7.7 ^c	-7.5 ^c	-6.6 ^c
C-01-74^b						
Travoprost ophthalmic solution containing BAC	25.3	-	24.3	-6.9	-	-6.7
Latanoprost/ timolol	24.6	-	23.9	-6.4	-	-6.1

^aThe C-97-79 IOP measurements were taken at 9 AM, 11 AM and 4 PM.

^bThe C-01-74 IOP measurements were taken at 9 AM and 5 PM.

^cp<0.05 for between group comparisons versus travoprost ophthalmic solution containing BAC.

A 9-month pivotal clinical study with a 5-year extension phase was conducted to evaluate the long-term safety of once-daily evening dosing of travoprost ophthalmic solution containing BAC.⁷ Overall, 196 patients were enrolled into the 5-year extension clinical trial, 67 of which were exposed to travoprost ophthalmic solution, 0.004% containing BAC. Travoprost ophthalmic solution containing BAC maintained clinically relevant long term IOP control in all patients for nearly 6 years. The overall incidence of iris discoloration in patients treated with travoprost ophthalmic solution containing BAC was 11.9%. The adverse events of iris discoloration were mild and did not interrupt patient continuation in the study. The observation of increased iris discoloration did not affect the incidence, nature or severity of adverse events recorded in the study. IOP reduction was similar regardless of the development of increased iris discoloration.

In a 3 month clinical study, **travoprost** dosed QD in the evening produced equivalent IOP lowering efficacy compared to travoprost ophthalmic solution containing BAC QD. The maximum mean IOP reductions for **travoprost** (8.5 mmHg) and travoprost ophthalmic solution containing BAC (8.4 mmHg) correspond to approximate 31% IOP reductions in each group. All mean reductions were clinically relevant and statistically significant (p<0.0001).

DETAILED PHARMACOLOGY

⁷ Sandoz Travoprost is a benzalkonium chloride-free formulation of travoprost ophthalmic solution containing BAC

Travoprost is a PGF_{2α} analogue. It is the (+) isomer of fluprostenol isopropyl ester and the prodrug of the active free acid constituent.

In Vitro Studies

Receptor Binding:

Receptor binding affinity was compared for the acid forms of travoprost and latanoprost. The two acid prostaglandin analogues had a high affinity binding for the FP-receptors (bovine corpus luteum membranes). Receptor interaction appeared to be at a single binding site. There was a low affinity for the other prostaglandin receptors. The parent free acid of travoprost is over 60-fold less potent in binding to other receptors. Travoprost demonstrates higher potency and higher selectivity for the FP receptor compared to latanoprost.

Receptor Affinity Data for Travoprost and Latanoprost Free Acids (K_i, nM)

	DP receptors	EP3 receptors	EP4 receptors	FP receptors	IP receptors	TP receptors
Travoprost free acid	46000	3500	12000	52	90000	120000
Latanoprost free acid	26000	7900	9000	92	> 90000	61000

Prostaglandin Functional Assays:

Travoprost free acid was a potent and fully efficacious agonist in stimulating phosphoinositide (PI) turnover in Swiss 3T3 cells expressing a FP receptor. In contrast, latanoprost acid had lower potency than the travoprost free acid and was a partial agonist in this system.

Second Messenger Study: Potency & Efficacy

	FP PI turnover	DP cyclase stim	EP2 cyclase stim
Travoprost free acid	4 nM (E _{max} = 100%)	Inactive	Inactive
Latanoprost free acid	27 nM (E _{max} = 75%)	Inactive	Inactive

Travoprost acid did not demonstrate affinity for a panel over 32 different non-prostanoid receptors including muscarinic, alpha-adrenergic, beta-adrenergic, and endothelin receptors at concentrations up to 10 μM.

Animal Pharmacology

In the cynomolgus monkey, instillation of a single dose of travoprost reduced IOP in a dose-related fashion, with a peak reduction of 30% with a 0.3 mcg dose. Once daily dosing provided IOP reductions for a 24 hour period.

Reductions of IOP Following b.i.d. Travoprost (AL-6221) in Laser Cynomolgus Monkeys

Dose (µg)	Baseline IOP	Dose number/hour after dose						
		Percent ± SEM (mmHg ± SEM)						
[Vehicle ¹]	(mmHg)	1/2 ²	1/4	1/6	4/16	5/2	5/4	5/6
0.1 [P/P]	36.8	1.8±6.4 (1.7±2.6)	7.7±6.8 (3.9±3.0)	9.3±8.1 (4.8±3.8)	16.9 ⁴ ±4.3 (6.8±1.9)	22.7 ⁴ ±5.8 (9.3±3.1)	21.8 ⁴ ±6.8 (9.2±3.5)	15.3±7.6 (6.6±3.6)
Vehicle	41.4	16.4±8.3 (8.4±5.1)	19.0±8.4 (10.2±2.6)	20.7±7.7 (10.6±3.0)	8.1±1.9 (3.8±6.1)	14.7±9.8 (8.4±3.3)	16.9±8.7 (9.0±3.4)	9.4±9.0 (6.4±3.0)
0.3 [T.N.]	41.6	19.0 ³ ±4.1 (8.5±1.9)	15.0 ³ ±2.5 (6.6±1.3)	18.5 ³ ±3.0 (8.2±1.5)	18.4 ³ ±5.9 (8.4±2.8)	31.2 ³ ±3.7 (13.5±2.1)	30.3 ³ ±3.8 (13.2±2.0)	26.6 ³ ±3.6 (11.6±1.9)
Vehicle	40.6	6.5±4.7 (3.2±2.5)	9.2±5.7 (4.0±3.7)	1.9±4.5 (9.0±3.8)	6.6 ⁴ ±2.6 (2.6±4.3)	13.3 ⁴ ±4.8 (5.4±4.0)	16.4±4.3 (7.2±2.0)	14.6±7.2 (7.0±1.6)
0.3 [P/P]	36.8	19.5 ³ ±3.7 (7.7±2.1)	25.7 ⁴ ±5.0 (10.8±3.4)	22.1 ⁴ ±5.9 (9.2±3.4)	29.9 ⁴ ±3.7 (11.9±2.4)	28.6 ⁴ ±5.2 (11.9±3.2)	28.1 ⁴ ±5.7 (11.9±3.4)	20.7 ⁴ ±5.3 (9.0±3.1)
Vehicle	34.7	7.2±4.8 (3.0±4.3)	6.1±7.0 (3.5±2.9)	5.1±8.1 (3.5±2.4)	2.6±5.6 (1.5±4.5)	1.1±6.0 (1.4±3.9)	4.6±7.5 (2.7±3.7)	6.8±6.7 (2.7±4.2)

¹P/P = phosphate buffered saline with polysorbate 80; T.N = Tears Naturale

²b.i.d. dosing at 0900 and 1700 hours; dose number/hour after dose

³p<0.01

⁴p<0.05

In one cross-over study, the optic nerve head blood flow (ONHBF) was significantly increased 13.4% (+ 3.9%) in 15 Dutch-belted rabbits following once-daily topical ocular dosing with travoprost 0.004% for one week. Systemic circulatory parameters were not affected by drug treatment.

Clinical Efficacy

Travoprost is a benzalkonium chloride-free formulation of travoprost ophthalmic solution containing BAC. Travoprost ophthalmic solution containing BAC dosed once-daily in patients with open-angle glaucoma or ocular hypertension, having a baseline mean intraocular pressure (IOP) between 25 to 27 mmHg, produced significant reductions in IOP when used either as a single therapy or adjunctively to TIMOPTIC* (timolol maleate ophthalmic solution) 0.5% BID.

Travoprost ophthalmic solution containing BAC, dosed QD in the evening, reduced IOP 6.7 to 9.0 mmHg. Stable 24-hour IOP reductions were achieved as early as 2 weeks after initiation of therapy and were maintained over the 6 to 12 month treatment period in three (3) well-controlled studies. The IOP reductions with Travoprost ophthalmic solution containing BAC were superior to those obtained with TIMOPTIC* and equal or better than those obtained with XALATAN* (latanoprost ophthalmic solution) 0.005% QD. Travoprost ophthalmic solution containing BAC demonstrated an earlier stabilization of IOP reduction and better overall IOP control over 24 hours compared to XALATAN*. Travoprost ophthalmic solution containing BAC was significantly more effective (up to 1.4 mmHg) than XALATAN* in reducing IOP in black patients.

A responder analysis (IOP reduction ≥ 30% or mean IOP < 17 mmHg), based on the data from the three pivotal studies, demonstrated that travoprost ophthalmic solution containing BAC had a significantly higher responder rate (56%) compared to XALATAN* (50%) which were both significantly greater than TIMOPTIC* (40%).

Responder Analyses Based on Percent IOP Reduction ($\geq 30\%$) or Mean IOP (≤ 17 mmHg)^a

Study Duration	Treatment Group		
	Travoprost ophthalmic solution, 0.004% containing BAC	TIMOPTIC* 0.5%	XALATAN* 0.005%
Study C-97-71 12 months	54.7 ^{1,2}	39	49.6 ³
Study C-97-72 6 months	50.5 ¹	65.4	Not applicable
Study C-97-79 9 months	63.3 ¹	47.1	Not applicable

^aResponse to therapy was based on IOP reduction $\geq 30\%$ from the corresponding diurnal baseline or a mean IOP ≤ 17 mmHg. The data is combined over visit and time of day and represents the percentage of patients that responded to therapy as defined above. Results are based upon the per protocol data sets.

¹ $p < 0.0001$ comparing Travoprost 0.004% vs. TIMOPTIC*.

² $p \leq 0.0163$ comparing Travoprost 0.004% vs. XALATAN*.

³ $p \leq 0.0106$ comparing XALATAN* vs. TIMOPTIC*.

In a 6-month well-controlled study, patients with a mean IOP of 24-26 mmHg on TIMOPTIC* BID who were treated with travoprost ophthalmic solution containing BAC dosed QD adjunctively to TIMOPTIC* demonstrated an additional 6-7 mmHg reduction in IOP.⁸

In a clinical pharmacology study patients were dosed one drop (travoprost ophthalmic solution containing BAC or **travoprost**) in each study eye at 8 PM for two weeks. **Travoprost** and travoprost ophthalmic solution containing BAC produced statistically significant and clinically relevant mean IOP reductions from baseline for up to 60 hours following the final dose of study drug. Mean IOP reductions, across the 5 post-dosing time points ranged from 4.9 to 8.2 mmHg for **travoprost** and from 5.2 to 8.6 mmHg for travoprost ophthalmic solution containing BAC. In addition, no safety issues were identified in a population of adult and elderly patients with open-angle glaucoma or ocular hypertension.

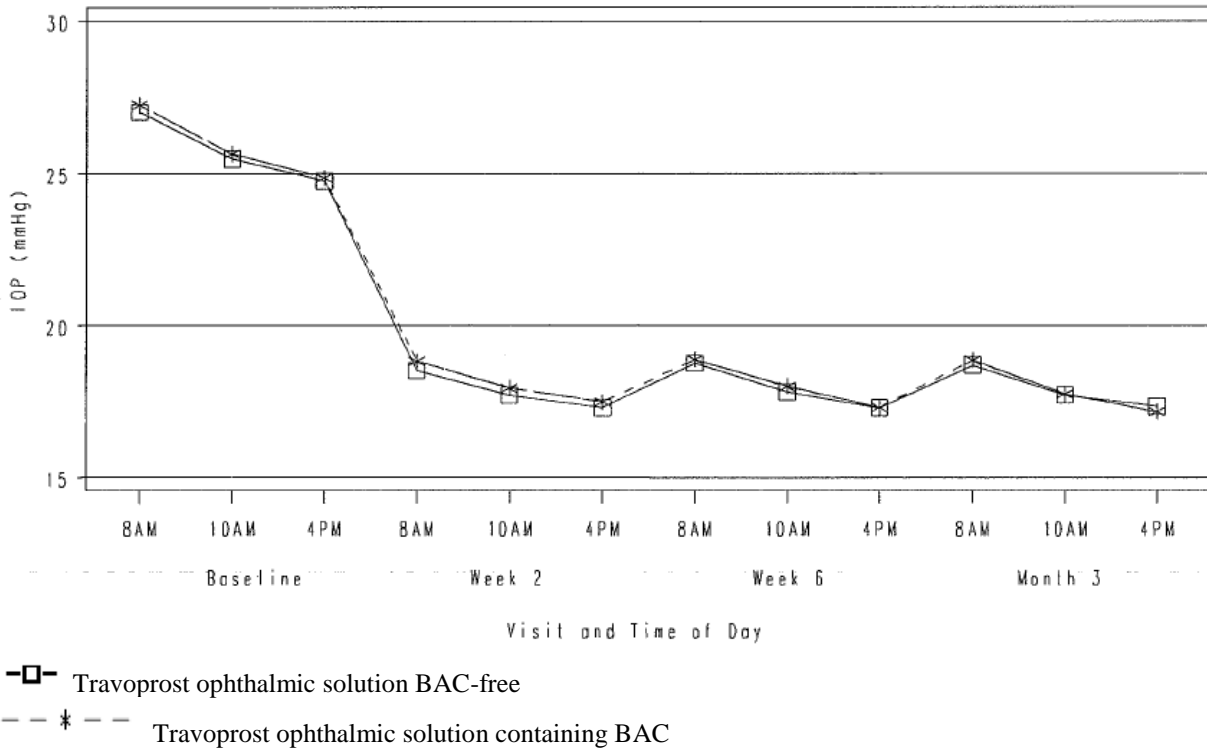
Travoprost, a benzalkonium chloride-free formulation of travoprost ophthalmic solution containing BAC, provides patients with open angle glaucoma or ocular hypertension with the additional potential benefit of decreasing their exposure to benzalkonium chloride and provides an alternative IOP-lowering treatment for patients intolerant to benzalkonium chloride.

In a 3-month clinical study, **travoprost** dosed QD in the evening produced statistically equivalent IOP lowering efficacy compared to travoprost ophthalmic solution containing BAC QD. Mean IOP reductions from baseline for **Travoprost** and travoprost ophthalmic solution containing BAC were clinically relevant and statistically significant at all measurement times. Mean IOP reductions in the per protocol and intent-to-treat analyses ranged from 7.3 to 8.5 mmHg for **Travoprost** and from 7.4 to 8.4 mmHg for travoprost ophthalmic solution containing BAC (Figure 1). The maximum mean IOP reductions for **Travoprost** (8.5 mmHg) and travoprost ophthalmic solution containing BAC (8.4 mmHg) correspond to approximate 31% IOP reductions in each group.

⁸ Sandoz Travoprost is a benzalkonium chloride-free formulation of travoprost ophthalmic solution containing BAC.

Travoprost and travoprost ophthalmic solution containing BAC provide similar IOP control, with up to 54% of patients in the **travoprost** group and up to 58% of patients in the travoprost ophthalmic solution containing BAC group achieving clinically relevant IOP response (IOP<18 mmHg).⁹ IOP response to treatment between groups was similar and not statistically significantly different at each study visit and time (p≥0.2198 across both analyses).

Figure 1: Mean IOP (mmHg) for travoprost and travoprost ophthalmic solution containing BAC



TOXICOLOGY

Acute Toxicity

Travoprost was demonstrated to have a low order of acute toxicity. No mortalities occurred in rats administered travoprost intravenously at a dose of 10 mg/kg (250,000-times the proposed clinical exposure) or in mice given up to 100 mg/kg/day (2,500,000-times the proposed clinical exposure). No significant systemic effects were observed.

Administration of travoprost ophthalmic solution, up to 0.01%, two drops every half-hour for five or six hours, did not result in any significant ocular or systemic effects.

Subchronic, Chronic Toxicity

Topical ocular administration of travoprost ophthalmic solution, 0.01%, three times a day for six months, in rabbits, resulted in no significant ocular or systemic effects. Iris pigmentation and a species specific increase in palpebral fissure and increase in lid retraction was observed in some monkeys receiving 0.0015%, 0.004% or 0.012% travoprost ophthalmic solution for up to one

⁹ Sandoz Travoprost is a benzalkonium chloride-free formulation of travoprost ophthalmic solution containing BAC.

year. No other significant ocular or systemic effects were seen.

Subchronic intravenous administration of travoprost in rats at all doses employed (100 to 1000 micrograms/kg/day) resulted in trace-to-moderate hyperostosis and bone fibrosis. Incidence and severity were dose related, and determined bone to be a target organ of toxicity in rats. Similar studies in mice resulted in no significant systemic effects at doses of up to 1000 mcg/kg/day.

Chronic systemic administration (subcutaneous) to rats at doses of 30 and 100 micrograms/kg/day resulted in dose-related hyperostosis and bone fibrosis similar to that observed in the subchronic study. No effect was observed in bone at 10 micrograms/kg/day (250-times the proposed clinical exposure), which was considered the no effect level.

Carcinogenesis

Two year bioassays, in which rats and mice were dosed with travoprost by subcutaneous injection at doses up to 100 micrograms/kg/day (2,500 times the clinical dose), revealed no evidence of carcinogenic effect.

Mutagenesis

Travoprost was not mutagenic in bacteria, in one mouse lymphoma assay, in the mouse micronucleus tests nor in the rat chromosome aberration assay. In another mouse lymphoma assay, higher concentrations of travoprost were slightly mutagenic only in the presence of activation enzymes.

Reproduction & Teratology

Travoprost did not affect mating or fertility indices in male or female rats and mice at subcutaneous doses up to 10 mcg/kg/day (250 times the recommended human dose). The mean number of corpora lutea was slightly reduced and an increase in post-implantation loss was detected at that dose, but was not affected at 3 mcg/kg/day (75 times the maximum recommended human dose).

In teratology studies conducted in pregnant rats and mice, travoprost reduced fetal viability when administered daily during the period of major organogenesis at doses as low as 1.0 (mice) and 10 (rats) mcg/kg/day (25 and 250 times the maximum recommended human dose, respectively) with the lowest no effect level at 0.3 mcg/kg/day (7.5 times the maximum recommended human dose). The incidence of skeletal malformations was slightly increased in fetuses of rat dams receiving travoprost by subcutaneous injection at 10 mcg/kg/day (250 times the maximum recommended human dose), but not at 3 mcg/kg/day (75 times the maximum recommended human dose). No fetal abnormalities were observed in mice at 1.0 mcg/kg/day (25 times the maximum recommended human dose).

Pregnant rats dosed subcutaneously with up to 0.72 mcg/kg/day from gestation Day 6 through lactation day 20 showed gestation length reduced in a dose related manner and the number of stillborn pups was increased. Surviving pup body weights were reduced. Pup development was affected as demonstrated by delayed static-righting reflex, eye opening and pinna detachment, delayed preputial separation and decrease in motor activity parameters. The no-observed adverse effect level was 0.1 mcg/kg/day (2.5 times the human recommended dose).

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**READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE
PATIENT MEDICATION INFORMATION**

**Pr Sandoz Travoprost
Travoprost Ophthalmic Solution, 0.004% w/v**

Read this carefully before you start taking Sandoz Travoprost and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **Sandoz Travoprost**.

What is Sandoz Travoprost used for?

Sandoz Travoprost is used to treat high pressure in the eye. This pressure can lead to an illness called **glaucoma**.

How does Sandoz Travoprost work?

High pressure in the eye. Your eyeballs contain a clear, watery liquid, which feeds the inside of the eye. Liquid is always emptying out of the eye, and more liquid is always being produced. If the eye fills up faster than it empties, the pressure inside the eye builds up. If it gets too high, it can damage your sight.

Sandoz Travoprost is one of a group of medicines for glaucoma which contain prostaglandin analogues. It works by increasing the outflow of liquid, which lowers the pressure in the eye. It may be used on its own or with other glaucoma eye drops, which also reduce pressure.

What are the ingredients in Sandoz Travoprost?

Medicinal ingredient: travoprost 0.040 mg/mL

Non-medicinal ingredients: sofZia[®] preservative system (boric acid, propylene glycol, sorbitol, zinc chloride), polyoxyl 40 hydrogenated castor oil, and purified water. Tiny amounts of hydrochloric acid or sodium hydroxide are added to maintain proper pH balance.

Sandoz Travoprost comes in the following dosage forms:

Liquid (a colourless to light yellow solution) supplied in a 2.5mL or 5mL plastic bottle with a screw cap.

Do not use Sandoz Travoprost if you are:

- Allergic (*hypersensitive*) to:
 - Travoprost.
 - Other prostaglandin analogues.
 - Other ingredients in **Sandoz Travoprost**. See **What are the ingredients in Sandoz Travoprost?**
- Pregnant or plan to become pregnant.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Sandoz Travoprost. Talk about any health conditions or problems you may have, including if you:

- Will be having eye surgery.
- Have an eye infection.
- Are breastfeeding or planning to breast-feed. **Sandoz Travoprost** may get into your breast milk.

Other warnings you should know about:

Sandoz Travoprost is not to be used by people under 18 years of age.

STOP taking Sandoz Travoprost and talk to your doctor immediately:

- If you develop an eye infection.
- Your eye(s) become irritated.
- You suffer any damage to your eye(s).

Take special care using Sandoz Travoprost Solution:

- **If you wear soft contact lenses.** Do not use **Sandoz Travoprost** while wearing contact lenses. Remove your contact lenses before applying **Sandoz Travoprost** and wait at least 15 minutes after using the drops before putting your lenses back in.
- **If your skin comes into contact with Sandoz Travoprost.** Wash your skin immediately. This is especially important for pregnant women.

Eye Effects

- **Sandoz Travoprost** may increase the length, thickness, colour and/or number of your eyelashes.
- **Sandoz Travoprost** may also change the colour of your eye. It may make your iris (the coloured part of your eye) more brown.
- If you use **Sandoz Travoprost** in one eye only, the possible change in colour in your iris, the skin around the eye or the change in the eyelashes may appear in the treated eye only.
- These changes in pigmentation and lash growth may be permanent.

Driving or using machines

You may find that your vision is blurred for a short time just after you use **Sandoz Travoprost**. Do not drive or use machines until your vision is clear.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

No drug interaction studies have been done with **Sandoz Travoprost**.

How to take Sandoz Travoprost:

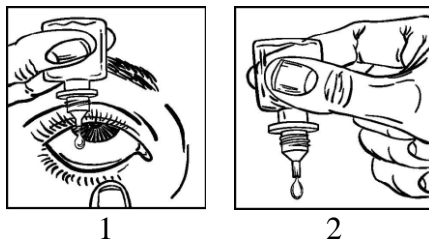
This medicine has been prescribed for you personally. You must not pass it on to other people. It may harm them even if they have the same illness as you.

Usual adult dose:

1 drop in the affected eye(s) once a day. Evening is the best time to take **Sandoz Travoprost**.

Only use **Sandoz Travoprost** in both eyes if your doctor told you to. Take it for as long as your doctor told you to.

Only use **Sandoz Travoprost** in your eyes.

**How to use:**

- Get the **Sandoz Travoprost** bottle and a mirror (if needed).
- Wash your hands.
- Twist off the cap.
- Hold the bottle, pointing down, between your thumb and fingers.
- Tilt your head back. Pull down your eyelid with a clean finger, until there is a 'pocket' between the eyelid and your eye. The drop will go in here (picture 1).
- Bring the bottle tip close to the eye. Use the mirror if it helps.
- Don't touch your eye or eyelid, surrounding areas or other surfaces with the dropper. It could get germs on the dropper tip.
- Gently squeeze the bottle to release one drop of **Sandoz Travoprost** at a time (picture 2).
- If you take drops in both eyes, repeat the steps for your other eye.
- Put the bottle cap back on tightly after use.

If a drop misses your eye, wipe it off with a tissue and try again.

If you are using other eye drops, wait at least 5 minutes between putting in **Sandoz Travoprost** and the other drops.

Overdose:

If you accidentally use too many drops, just go back to your regular once a day dosing the next day. If you have any concerns, talk to your doctor or pharmacist.

If you think you have taken too much **Sandoz Travoprost**, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

If you forget to use **Sandoz Travoprost**, take your next scheduled dose. Do not use a double dose to make up the missed dose.

What are possible side effects from using Sandoz Travoprost?

These are not all the possible side effects you may feel when taking **Sandoz Travoprost**. If you experience any side effects not listed here, contact your healthcare professional.

Side effects in the eye may include:

- Eye redness.
- Burning or stinging eyes.
- Itchy eyes.
- A change in eye colour.
- Dry eyes.
- A feeling that something is in the eyes.
- Eye or eyelid inflammation (swelling).
- Eye pain.
- Blurred or reduced vision.
- Sensitivity to light.
- Eye discharge.
- Eczema (rash) on the eyelids.
- Eyelid itching, crusting, redness or irritation.
- Increased tearing.
- Change in eyelash colour, eyelash thickening, growth or loss.
- Abnormally positioned eyelashes that grow back toward the eye.
- Reduced feeling in the eyes.
- Tired eyes, eye allergy, or sunken eyes.

Other side effects in the body:

- Headache
- Skin darkening or discolouration.
- Dizziness.
- A bad taste in the mouth
- High or low blood pressure.
- Cold-like symptoms, such as cough, voice disorder, throat pain, or nose discomfort.
- Dry nose or mouth.
- Nasal allergy or inflammation (swelling).
- Nose bleeds.
- Constipation, abdominal pain, nausea, vomiting or diarrhea.
- Excessive hair growth or hair colour changes.
- Rash, skin redness or itching.
- Feeling weak.
- Depression, trouble sleeping (insomnia) or anxiety.
- A ringing in the ears.
- Chest or joint pain.
- Muscle pain.
- Increase in prostate cancer marker.

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
UNCOMMON or RARE Eye problems: clouded, blurry or dim vision, trouble seeing at night, sensitivity to light, halos around lights, fading or “yellowing” of colours, eye pain, eye redness, feeling like there is something in your eye, tearing, rash or sores on the eyelids or around the eyes		√	
UNCOMMON Allergic reaction: rash, hives, swelling of the face, lips, tongue or throat, difficulty swallowing or breathing			√
RARE Heart problems: fast or slow heartbeat UNKNOWN Heart problems: abnormal or irregular heartbeat		√	
RARE Breathing problems: asthma, shortness of breath			√
UNKNOWN Bladder problems: loss of bladder control, painful urination		√	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (<https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html>) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Store at 2°C - 25°C. No refrigeration required.

Don't use the drops after the expiry date (marked 'Exp') on the bottle and the box.

Keep out of reach and sight of children.

If you want more information about Sandoz Travoprost:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (<https://health-products.canada.ca/dpd-bdpp/index-eng.jsp>); the manufacturer's website <http://www.sandoz.ca>, or by calling 1-800-361-3062.

This leaflet was prepared by Sandoz Canada Inc.

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