PRODUCT MONOGRAPH

[Pr]pms-TRAVOPROST Z

Travoprost Ophthalmic Solution, USP
0.004% w/v

Elevated Intraocular Pressure Therapy
Prostaglandin $F_{2\alpha}$ analogue

PHARMASCIENCE INC.
6111 Royalmount Ave., Suite 100
Montreal, Quebec
H4P 2T4

www.pharmascience.com

Date of Revision:
May 25, 2016

Submission Control No.: 194893

PRODUCT MONOGRAPH

[Pr]pms-TRAVOPROST Z
Travoprost Ophthalmic Solution, USP

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.

Pharmacokinetics/ Pharmacodynamics

Travoprost ophthalmic solution, 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.

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 ^{14}C-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.

Clinical Studies

Travoprost ophthalmic solution is a benzalkonium chloride-free formulation. 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 solution. Travoprost solution 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 timolol (timolol maleate) 0.5% BID, who were treated with travoprost solution dosed QD adjunctively to timolol (timolol maleate) 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 timolol (timolol maleate) 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 timolol (timolol maleate) 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 timolol (timolol maleate) 0.5% dosed BID	1 drop QD (8 PM) of travoprost 0.004% or 0.0015% plus 1 drop BID of open-label timolol (timolol maleate) 0.5% (8 AM and 8 PM); or 1 drop WD (8 PM) of placebo plus 1 drop BID of open-label timolol (timolol maleate) 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 timolol (timolol maleate) 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	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	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 / 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	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	25.3	--	24.3	-6.9	--	-6.7
latanoprost / timolol	24.6	--	23.9	-6.4	--	-6.1

[a] The C-97-79 IOP measurements were taken at 9 AM, 11 AM and 4 PM.

[b] The C-01-74 IOP measurements were taken at 9 AM and 5 PM.

[c] $p<0.05$ for between group comparisons versus travoprost.

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 solution[1]. Overall, 196 patients were enrolled into the 5-year extension clinical trial, 67 of which were exposed to travoprost solution. Travoprost solution 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 solution 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 solution benzalkonium chloride-free formulation dosed QD in the evening produced equivalent IOP lowering efficacy compared to travoprost solution QD. The maximum mean IOP reductions for travoprost solution benzalkonium chloride-free formulation (8.5 mmHg) and travoprost solution (8.4 mmHg) correspond to approximate 31% IOP reductions in each group. All mean reductions were clinically relevant and statistically significant ($p<0.0001$).

INDICATIONS AND USAGE

pms-TRAVOPROST Z 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 pms-TRAVOPROST Z have not been established in pediatric patients, and its use is not recommended in these patients.

CONTRAINDICATIONS

pms-TRAVOPROST Z 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 PHARMACEUTICAL INFORMATION – Composition and AVAILABILITY OF DOSAGE FORMS.

pms-TRAVOPROST Z 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

pms-TRAVOPROST Z is a benzalkonium chloride-free formulation. In phase III clinical trials, travoprost solution was studied adjunctively with timolol (timolol maleate). No additional adjunctive studies have been done.

[1] Formulation containing benzalkonium chloride.

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 pms-TRAVOPROST Z, the patient must wait until vision clears before driving or using machinery.

Hepatic/Renal
Travoprost solution 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 m^2 to 77 mL/min/1.73 m^2). 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 pms-TRAVOPROST Z in inflammatory ocular conditions; nor in neovascular or angle-closure glaucoma.

pms-TRAVOPROST Z should be used with caution in patients with active intraocular inflammation (iritis/uveitis).

Patients should remove contact lenses prior to administration of pms-TRAVOPROST Z. Lenses may be reinserted 15 minutes following administration of pms-TRAVOPROST Z.

Macular edema: Macular edema, including cystoid macular edema, has been reported during treatment with prostaglandin F2α 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. pms-TRAVOPROST Z 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 advice concerning the continued use of the multi-dose container.

Ocular Effects: Travoprost ophthalmic solution benzalkonium chloride-free formulation 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 solution beyond five years[2].

Periorbital and/or eyelid skin darkening has been reported in association with the use of travoprost ophthalmic solution benzalkonium chloride-free formulation.

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

Travoprost ophthalmic solution benzalkonium chloride-free formulation 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 sternebrae, domed head and hydrocephaly. No effect was observed at 3 mcg/kg/day (75 times the maximum recommended human dose of 0.04 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

[2] Formulation containing benzalkonium chloride.

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 pms-TRAVOPROST Z 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*.

pms-TRAVOPROST Z is a benzalkonium chloride-free formulation. Ocular hyperemia was reported in 40% of all patients receiving travoprost solution and travoprost ophthalmic solution benzalkonium chloride-free formulation. 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 solutions.

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 ≥ 1.0%

	Travoprost 0.004% n=656		Travoprost 0.004% + 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	3	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
Nonocular				
Body as a Whole				
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
Cardiovascular System				
Hypertension	27	4.1	2	1.4
Digestive System				
GI disorder	10	1.5	1	0.7
Metabolic and Nutritional				
Hypercholesteremia	11	1.7	0	
Nervous System				
Depression	9	1.4	2	1.4
Respiratory System				
Sinusitis	11	1.7	3	2.1
Bronchitis	7	1.1	1	0.7
Rhinitis	7	1.1	1	0.7
Urogenital System				
Infection urinary tract	7	1.1	3	2.1

	Travoprost 0.004% n=656		Travoprost 0.004% + Timolol 0.5 % n=145	
	n	%	n	%
Prostate disorder	6	0.9	2	1.4

[3] Increase in brown pigmentation of the iris

[4] Lid pigment (1)

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

A similar safety profile was observed in a clinical trial of three months duration, comparing therapy with travoprost solution benzalkonium chloride-free formulation (399 patients dosed QD in the evening) to travoprost solution (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 solution in clinical practice and in the literature have been included based on the frequency of reporting, possible causal connection to travoprost solution, 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 solution[7] and travoprost solution benzalkonium chloride-free formulation 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 discolouration, eyelash thickening, eyelid irritation, eyelid margin crusting, eyelid pruritis, growth of eyelashes, hypoaesthesia eye, iridocyclitis, periorbital edema, punctate keratitis;
Gastrointestinal disorders: constipation, dry mouth;
General disorders and administration site conditions: asthenia;
Nervous system disorders: dizziness, dysgeusia;
Respiratory, thoracic and mediastinal disorders: cough, nasal discomfort, nasal dryness, oropharyngeal pain;
Skin and subcutaneous tissue disorders: hair colour changes, hypertrichosis, madarosis, rash, skin discolouration, skin hyperpigmentation.
Adverse reactions identified from post-marketing surveillance include the following:
Ear and labyrinth disorders: tinnitus;
Eye disorders: sunken eyes;
Gastrointestinal disorders: abdominal pain, diarrhea, nausea;
Investigations: prostate specific antigen increased;
Musculoskeletal and connective tissue disorders: arthralgia, musculoskeletal pain;

[6] Formulation containing benzalkonium chloride.
[7] Formulation containing benzalkonium chloride.

Psychiatric disorders: anxiety;
Renal and urinary disorders: dysuria, urinary incontinence;
Skin and subcutaneous tissue disorders: erythema, pruritis;
Vascular disorders: hypotension.

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. 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, drug-lifestyle interactions have not been established.

SYMPTOMS & TREATMENT OF 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 pms-TRAVOPROST Z occurs, treatment should be symptomatic.

For management of a suspected drug overdose, contact your regional Poison Control Centre immediately.

DOSAGE AND ADMINISTRATION

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

pms-TRAVOPROST Z 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 contaminated solutions.

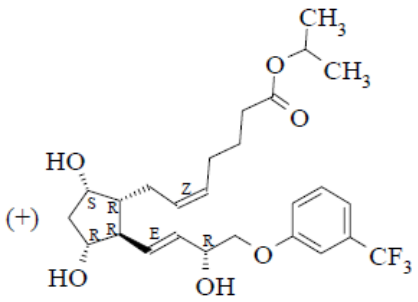
PHARMACEUTICAL INFORMATION

Drug Substance:

Proper name: Travoprost

Chemical name: Isopropyl (Z) -7-[(1R,2R,3R,5S)-3,5-dihydroxy-2-[(1E,3R)-3-hydroxy-4[(α,α,α-trifluoro-m-tolyl)oxy]-1-butenyl]cyclopentyl]-5-heptenoate

Structural formula:



Molecular Formula: $C_{26}H_{35}F_3O_6$.

Molecular Weight: 500.6 g/mol

Description: Travoprost is viscous liquid oil

Solubility: Freely soluble in acetone and methanol. Practically insoluble in water.

Composition:

pms-TRAVOPROST Z 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 pms-TRAVOPROST Z contains:
Medicinal ingredient: 40 mcg travoprost.
Non-medicinal ingredients: polyoxyl 40 hydrogenated castor oil, purified water, 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.

Stability and Storage Recommendations: Store between 2°C to 30°C. Protect from light. Discard 28 days after opening. Keep out of reach and sight of children.

AVAILABILITY OF DOSAGE FORMS

pms-TRAVOPROST Z is a sterile, buffered, preserved, aqueous solution supplied in the plastic dispenser bottle, containing 2.5 mL or 5 mL.

INFORMATION FOR THE CONSUMER

[Pr]pms-TRAVOPROST Z

Travoprost Ophthalmic Solution, USP
0.004% w/v

Medicine to treat Elevated Intraocular Pressure

Information for the Patient: pms-TRAVOPROST Z.

Read all of this leaflet carefully before you start using this medicine.

Keep this leaflet. You may need to read it again. If you still have questions after reading it, please ask your doctor or your pharmacist.

The active substance is travoprost 0.040 mg/mL.

Other ingredients: Preservative: 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.

1. WHAT pms-TRAVOPROST Z DOES

pms-TRAVOPROST Z is used to treat high pressure in the eye. This pressure can lead to an illness called **glaucoma**.

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.

pms-TRAVOPROST Z 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.

pms-TRAVOPROST Z is a liquid (a colourless to light yellow solution) supplied in a 2.5mL or 5mL plastic bottle with a screw cap.

2. BEFORE YOU USE pms-TRAVOPROST Z

Do not use pms-TRAVOPROST Z:

- **If you are allergic** (*hypersensitive*) to travoprost, prostaglandin analogues or any of the other ingredients in pms-TRAVOPROST Z (see Other Ingredients).
- If you are pregnant, or planning to become pregnant.

Before you use pms-TRAVOPROST Z, talk to your doctor or pharmacist if you:
- Will be having eye surgery.
- Have an eye infection.
- Are breastfeeding or planning to breast-feed. pms-TRAVOPROST Z may get into your breast milk.

pms-TRAVOPROST Z is not to be used by people under 18 years of age.

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

Eye Effects
- **pms-TRAVOPROST Z** may increase the length, thickness, colour and/or number of your eyelashes.
- **pms-TRAVOPROST Z** may also change the colour of your eye. It may make your iris (the coloured part of your eye) more brown.
- If you use **pms-TRAVOPROST Z** 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 **pms-TRAVOPROST Z**. Do not drive or use machines until your vision is clear.

Interactions with this medication
Please tell your doctor or pharmacist if you are taking (or recently took) any other medicines. Also mention those medicines that you bought without prescription.

No drug interaction studies have been done with pms-TRAVOPROST Z.

3. HOW TO USE pms-TRAVOPROST Z

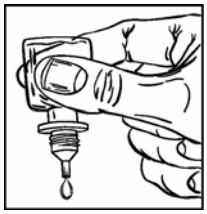
This medicine has been prescribed for you personally. You must not pass it on to other people. It may harm them even if they have the same illness as you.

Usual adult dose:

1 drop in the affected eye(s) once a day. Evening is the best time to take pms-TRAVOPROST Z.

Only use **pms-TRAVOPROST Z** in both eyes if your doctor told you to. Take it for as long as your doctor told you to.

Only use **pms-TRAVOPROST Z** in your eyes.



How to use:
- Get the **pms-TRAVOPROST Z** 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 **pms-TRAVOPROST Z** 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 pms-TRAVOPROST Z and the other drops.

Missed Dose
If you forget to use pms-TRAVOPROST Z, take your next scheduled dose. Do not use a double dose to make up the missed dose.

Overdosage

In case of drug overdose, particularly accidental oral ingestion, contact your doctor, hospital emergency department, or regional poison control centre, even if there are no symptoms.

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.

4. POSSIBLE SIDE EFFECTS

Some people who use pms-TRAVOPROST Z may have side effects. They can be unpleasant, but most of them soon pass.

You can usually carry on taking the drops, unless the effects are serious. If you're worried, talk to your doctor or pharmacist.

Common side effects
The following may affect approximately 1 in every 3 people.
Redness of the eye. Approximately 80 to 90% of the redness reported in clinical trials was mild and lessened over time without treatment.

One or more of these may affect approximately 5 in every 100 people.
Effects in the eye: burning or stinging upon instillation, itchy eye, change of colour of the iris, dry eye, foreign body sensation, eye or eyelid inflammation, pain in the eye, blurred vision, decreased vision, sensitivity to light.
Effects in the body: headache.

Other side effects
Other side effects may include:
Effects in the eye: reduced vision, clouding of the eye, swelling around the eye, eye discharge, eyelid itching, eyelid crusting, increased tearing, eyelid redness, growth of eyelashes, eye swelling, decreased eye sensation, tired eyes, eye allergy, eyelid irritation, eyelash discolouration, loss of eyelashes, sunken eyes
Effects in the body: allergy, skin darkening, dizziness, bad taste in the mouth, heart rate decreased, irregular heart beat, high blood pressure, asthma, shortness of breath, cough, throat irritation, nose discomfort, nasal dryness, dry mouth, constipation, skin discolouration, excessive hair growth, hair colour changes, rash, body weakness, depression, anxiety, ringing in ears, chest pain, decreased blood pressure, abdominal pain, nausea, skin redness, itching, joint pain, diarrhea, painful or involuntary urination

If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

Reporting Side Effects
You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.
3 ways to report:

- Online at MedEffect (www.healthcanada.gc.ca/medeffect);
- By calling 1-866-234-2345 (toll-free);
- By completing a Consumer Side Effect Reporting Form and sending it by:
  - Fax to 1-866-678-6789 (toll-free), or
  - Mail to: Canada Vigilance Program
    Health Canada, Postal Locator 0701E

Ottawa, ON
K1A 0K9

Postage paid labels and the Consumer Side Effect Reporting Form are available at MedEffect (www.healthcanada.gc.ca/medeffect).

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.

5. STORING pms-TRAVOPROST Z

Keep out of the reach and sight of children.

Store at 2°C - 30°C. Protect from light. Discard 28 days after opening. No refrigeration required.

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

If you have any other questions about your medicines you should ask a doctor or pharmacist.

6. MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be obtained by contacting Pharmascience Inc. at: 1-888-550-6060.

This leaflet was prepared by.

Pharmascience Inc.
Montréal Canada
H4P 2T4
www.pharmascience.com

PHARMACOLOGY

Travoprost is a $PGF_{2\alpha}$ 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 (Ki, 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 (Emax = 100%)	Inactive	Inactive
Latanoprost free acid	27 nM (Emax = 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 mcM.

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 (mcg) [Vehicle[1]]	Baseline IOP (mmHg)	Dose number/hour after dose Percent ± SEM (mmHg ± SEM) 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[4] ± 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)

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

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

3 $p<0.01$

4 $p<0.05$

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 ophthalmic solution is a benzalkonium chloride-free formulation. Travoprost ophthalmic solution 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 timolol (timolol maleate ophthalmic solution) 0.5% BID.

Travoprost solution, 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 solution were superior to those obtained with timolol (timolol maleate) and equal or better than those obtained with latanoprost (latanoprost ophthalmic solution) 0.005% QD. Travoprost solution demonstrated an earlier stabilization of IOP reduction and better overall IOP control over 24 hours compared to latanoprost 0.005%. Travaprost solution was significantly more effective (up to 1.4 mmHg) than latanoprost 0.005% in reducing IOP in black patients.

A responder analysis (IOP reduction $\geq$ 30% or mean IOP $\leq$ 17 mmHg), based on the data from the three pivotal studies, demonstrated that travaprost solution had a significantly higher responder rate (56%) compared to latanoprost 0.005% (50%) which were both significantly

greater than timolol (timolol maleate) (40%).

Responder Analyses Based on Percent IOP Reduction (≥30%) or Mean IOP (≤17 mmHg)[a]

Study Duration	Treatment Group		
	TRAVOPROST 0.004%	TIMOLOL (TIMOLOL MALEATE) 0.5%	LATANOPROST 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]	35.4	Not applicable
Study C-97-79 9 months	63.3[1]	47.1	Not applicable

[a] Response to therapy was based on IOP reduction ≥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. Timolol (timolol maleate).

[2] $p\leq0.0163$ comparing Travoprost 0.004% vs. Latanoprost.

[3] $p\leq0.0106$ comparing Latanoprost vs. Timolol (timolol maleate).

In a 6-month well-controlled study, patients with a mean IOP of 24-26 mmHg on timolol (timolol maleate) 0.5% BID who were treated with travoprost solution[8] dosed QD adjunctively to timolol (timolol maleate) demonstrated an additional 6-7 mmHg reduction in IOP.

In a clinical pharmacology study patients were dosed one drop (travoprost solution or travoprost solution benzalkonium chloride-free formulation) in each study eye at 8PM for two weeks. Travoprost solution or travoprost solution benzalkonium chloride-free formulation 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 solution benzalkonium chloride-free formulation and from 5.2 to 8.6 mmHg for travoprost solution. In addition, no safety issues were identified in a population of adult and elderly patients with open-angle glaucoma or ocular hypertension.

pms-TRAVOPROST Z, a benzalkonium chloride-free formulation, 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.

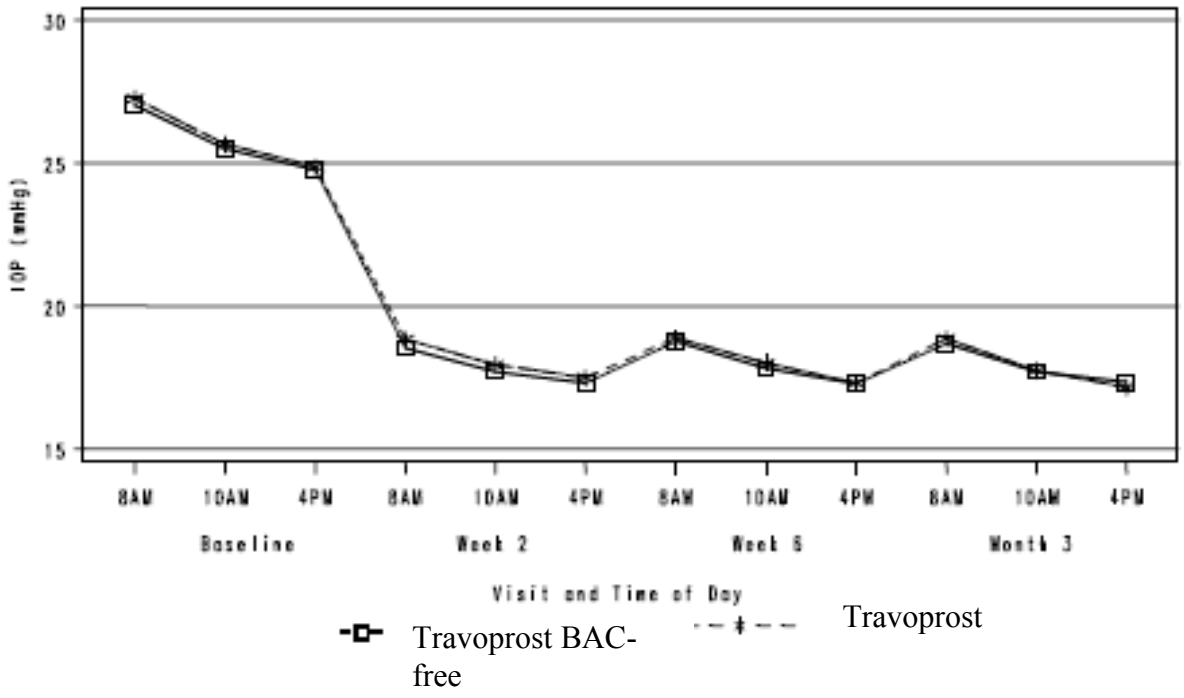
In a 3 month clinical study, travoprost solution benzalkonium chloride-free formulation dosed QD in the evening produced statistically equivalent IOP lowering efficacy compared to travoprost solution QD. Mean IOP reductions from baseline for travoprost solution benzalkonium chloride-free formulation and travoprost solution 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 solution benzalkonium chloride-free formulation and from

[8] Formulation containing benzalkonium chloride.

7.4 to 8.4 mmHg for travoprost solution (Figure 1). The maximum mean IOP reductions for travoprost solution benzalkonium chloride-free formulation (8.5 mmHg) and travoprost solution (8.4 mmHg) correspond to approximate 31% IOP reductions in each group.

Travoprost solution benzalkonium chloride-free formulation and travoprost solution provide similar IOP control, with up to 54% of patients in the travoprost solution benzalkonium chloride-free formulation group and up to 58% of patients in the travoprost solution group achieving clinically relevant IOP response (IOP<18 mmHg). IOP response to treatment between groups was similar and not statistically significantly different at each study visit and time ($p \geq 0.2198$ across both analyses).

Figure 1: Mean IOP (mmHg) for Travoprost solution benzalkonium chloride-free formulation and Travoprost solution



Travoprost BAC-free = Travoprost solution benzalkonium chloride-free formulation

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

Subchronic intravenous administration of travoprost in rats at all doses employed (100 to 1000 mcg/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 mcg/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 mcg/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 mcg/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).

REFERENCES

1. Goldberg I, Cunha-Vaz J, Jakobsen J-E, Nordmann JP, Trost E, Sullivan EK, The International Travoprost Study Group. Comparison of Topical. Travoprost eye drops given once daily and timolol 0.5% given twice daily in patients with open-angle glaucoma or ocular hypertension. J Glaucoma 2001; 10: 414-422

2. Gross R, Peace JH, Smith SE, Walters TR, DuBiner HB, Weiss MJ, Ochsner KI, Duration of IOP reduction with travoprost BAK-free solution. J Glaucoma 2008; 17(3): 217-222.

3. Lewis RA et al. Travoprost 0.004% With and Without Benzalkonium Chloride: A Comparison of Safety and Efficacy. J Glaucoma 2007; 16(1): 98-103.

4. Netland PA, Landry T, Sullivan EK, Andrew R, Silver L, Weiner A, Mallick S, Dickerson J, Bergamini MVW, Robertson SM, Davis AA. The Travoprost Study Group. Travoprost compared with latanoprost and timolol in Patients with open-angle glaucoma or ocular hypertension. Am J Ophthalmol 2001; 132: 472-484.

5. Orengo-Nania S, Landry T, von Tress M, Silver L, Weiner A, Davis AA, The Travoprost Study Group. Evaluation of Travoprost as adjunctive therapy in patients with uncontrolled intraocular pressure while using timolol 0.5%. Am J Ophthalmol 2001; 132: 860-868.

6. Sharif NA, Davis TL, Williams GW. [3H]AL-5848 (3[H] 9p-(+)-Fluprostenol). Carboxylic acid of Travoprost (AL-6221), a novel FP prostaglandin to study the pharmacology and autoradiographic localization of the FP receptor. J Pharm Pharmacol 1999; 51: 685-694.

7. Sorbera L, Castaner J (2000). Travoprost. Drugs Future 25 (1): 41-45.

8. Konstas AGP, Mikropoulos O, Kaltsos K, Jenkins IN, Stewart WC. 24-hour intraocular pressure control obtained with evening versus morning dosed travoprost in primary open angle glaucoma. Ophthalmology 2006; 113(3): 446-450.

9. Fellman RL, Sullivan EK, Ratliff M, Silver LH, Whitson JT, Turner FD, Weiner AL, Davis AA, The Travoprost Study Group. Comparison of Travoprost 0.0015% and 0.004% with Timolol 0.5% in Patients with Elevated Intraocular Pressure – A 6-month, Masked, Multicenter trial. Ophthalmology 2002; 109(5) 998-1008.

10. The AGIS Investigators. The Advanced Glaucoma Intervention Study (AGIS): 7. The relationship between control of intraocular pressure and visual field deterioration. Am J Ophthalmol 2000;130(4):429-40.

11. [Pr]TRAVATAN® Z Product Monograph, Alcon Canada Inc., Control Number: 188469, Date of Revision: January 21, 2016.