PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

Pr APO-TRAVOPROST

Travoprost Ophthalmic Solution USP

0.003% w/v

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

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	All Nonmedicinal Ingredients
Ophthalmic (topical)	Solution / 0.003% travoprost	Preservative: polyquaternium-1 0.01 mg/mL; Inactives: boric acid, mannitol, polyoxyl 40 hydrogenated castor oil, propylene glycol, sodium chloride, sodium hydroxide and/or hydrochloric acid (to adjust pH) and water for injection.

INDICATIONS AND CLINICAL USE

APO-TRAVOPROST, 0.003% w/v, is indicated for the reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension.

Geriatrics (> 65 years of age):
No overall differences in safety and effectiveness have been observed between elderly and other adult patients.

Pediatrics (< 18 years of age):
The safety and efficacy of travoprost ophthalmic solution, 0.003% has not been established in pediatric populations. Therefore, APO-TRAVOPROST is not recommended in these patients.

CONTRAINDICATIONS

APO-TRAVOPROST should not be used in the following:

- Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see the **DOSAGE FORMS, COMPOSITION AND PACKAGING** section of the product monograph.

- Patients who are pregnant or attempting pregnancy.

WARNINGS AND PRECAUTIONS

General
FOR OPHTHALMIC USE ONLY

Patients should remove contact lenses prior to administration of APO-TRAVOPROST, 0.003%; lenses may be reinserted 15 minutes following administration.

Carcinogenesis and Mutagenesis
See **TOXICOLOGY** section for animal data.

Dependence/Tolerance
No evidence of drug abuse, withdrawal or rebound phenomena has been identified with the use of travoprost in clinical trials.

Driving and Using Machinery
The instillation of APO-TRAVOPROST, 0.003% may cause temporary blurred vision and other visual disturbances, which may affect the ability to drive or use machines. If blurred vision occurs after instillation, the patient should be advised to wait until vision clears before driving or using machinery.

Ophthalmologic
APO-TRAVOPROST, 0.003% may gradually change eye colour, 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 colour 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 colour has predominantly been seen in patients with mixed coloured irises i.e., blue-brown, gray-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 colour change.

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.

Periorbital and/or eyelid skin darkening has been reported in association with the use of travoprost ophthalmic solution (0.004%).

APO-TRAVOPROST, 0.003% 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.

There is no experience with travoprost ophthalmic solution, 0.003% in inflammatory ocular conditions, or in neovascular or angle-closure glaucoma.

APO-TRAVOPROST, 0.003% should be used with caution in patients with active intraocular inflammation (iritis/uveitis), as well as patients with predisposing risk factors for uveitis.

Macular edema, including cystoid macular edema, has been reported during treatment with prostaglandin $F_{2\alpha}$ analogues. These reports have mainly occurred in aphakic patients, pseudophakic patients with a torn posterior lens capsule, or in patients with known risk factors for macular edema. APO-TRAVOPROST, 0.003% should be used with caution in these patients.

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.

Renal/Hepatic
Travoprost ophthalmic solution, 0.004%, 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/1.737m^2 to 77 mL/min/1.73m^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.

Sexual Function/Reproduction
There are no data on the effects of travoprost ophthalmic solution, 0.003% on human fertility.

Special Populations

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 to 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 or fetal external, visceral or skeletal malformation was observed after 1.0 mcg/kg/day subcutaneous administration during gestation days 6 to16 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 APO-TRAVOPROST, 0.003% is administered to a nursing woman.

Pediatrics (< 18 years of age): The safety and efficacy of travoprost ophthalmic solution, 0.003% has not been established in pediatric populations. Therefore, travoprost ophthalmic solution, 0.003% is not recommended in these patients.

Geriatrics (> 65 years of age): No overall differences in safety and effectiveness have been observed between elderly and other adult patients.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Travoprost ophthalmic solution, 0.003% (polyquaternium-1 preserved) is a benzalkonium chloride-free (BAK-free) formulation containing a 25% lower concentration of travoprost relative to travoprost ophthalmic solution, 0.004% (BAK-preserved) and travoprost ophthalmic solution, 0.004% Z (ionic buffered system-preserved).

In a single clinical study, 442 patients were exposed to travoprost ophthalmic solution, 0.003% once daily (QD) versus 421 patients exposed to travoprost ophthalmic solution, 0.004% once daily (QD) for up to 3 months.

The majority of adverse events (AE) reported for either treatment group during the pivotal study were for local ocular effects with a known casual association with the use of travoprost and topical ocular prostaglandin analogs (PGAs) in general. As expected, lower exposure to travoprost resulted in a slightly lower incidence of adverse drug reactions (ADR) reported in patients dosing with travoprost ophthalmic solution, 0.003% versus travoprost ophthalmic solution, 0.004%. The most common ADR reported in the study was hyperemia of the eye (ADRs for ocular and conjunctival combined). The severity of hyperemia was similar between the 2 treatments groups as approximately 90% of the reports in each group were assessed as mild.

No Serious Adverse Event (SAE) assessed as related to the use of travoprost ophthalmic solution, 0.003% was reported in the study. The majority of SAEs reported were resolved during the course of the study, the use of study drug was not interrupted, and the patients completed the clinical study without further incidence of the SAE.

Overall, the safety profile of travoprost ophthalmic solution, 0.003% was similar to that of travoprost ophthalmic solution, 0.004% (BAK-preserved) in clinical trial C-11-034. Travoprost ophthalmic solution, 0.003% was associated with numerically less hyperemia than travoprost ophthalmic solution, 0.004% treatment over the course of the 3 month trial.

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.

Table 1 summarizes adverse events assessed by the examining physician as related to the use of test article (ADR) at an incidence of ≥ 1% reported in patients with exposure to travoprost ophthalmic solution, 0.003% (polyquaternium-1 preserved), relative to travoprost ophthalmic solution, 0.004% (BAK-preserved), in clinical trial C-11-034.

Table 1: Clinical Trial Adverse Drug Reactions ≥ 1% Reported with the Use of Travoprost Ophthalmic Solution, 0.003% and Corresponding Incidences Observed with Travoprost Ophthalmic Solution 0.004% (Study C-11-034)

	Travoprost Ophthalmic Solution, 0.003% (polyquaternium-1 preserved) n = 442		Travoprost Ophthalmic Solution, 0.004% (BAK-preserved) n = 421	
	N	%	N	%
Eye disorders				
Ocular hyperaemia	27	6.1	32	7.6
Conjunctival hyperaemia	25	5.7	29	6.9
Eye pruritus	12	2.7	8	1.9
Eye irritation	9	2.0	5	1.2
Dry eye	6	1.4	5	1.2

Travoprost Ophthalmic Solution, 0.003% = Travoprost 30 mcg/mL eye drops, solution preserved with polyquaternium-1
Travoprost Ophthalmic Solution, 0.004% Z = Travoprost 40 mcg/mL eye drops, solution preserved with benzalkonium chloride (BAK)

Less Common Clinical Trial Adverse Drug Reactions (< 1%)
The list below summarizes ADRs reported at an incidence of < 1% in clinical trial C-11-034. Adverse drug reactions are presented in alphabetical order within the System Organ Classification (SOC).

Eye disorders: anterior chamber cell, anterior chamber inflammation, blepharitis, conjunctivitis, conjunctivitis allergic, dark circles under eyes, erythema of eyelid, eye discharge, eyelid margin crusting, eyelid oedema, eye pain, eyelid pain, eyelid pruritus, eyelash thickening, foreign body sensation in eyes, growth of eyelashes, iritis, photophobia, punctate keratitis, vision blurred, visual impairment

Investigations: corneal staining

Nervous system disorders: dizziness, headache, somnolence

Skin and subcutaneous tissue disorders: pruritus, rash, skin discolouration

Post-Market Adverse Drug Reactions
Additional adverse drug reactions (ADRs) reported during the post-market use of travoprost ophthalmic solution, 0.004% via post-marketing surveillance and other clinical trials are summarized below.

Table 2 summarizes ADRs reported in other clinical trials involving travoprost ophthalmic solution, 0.004%. The duration of these studies ranged from 3 months (including 12 weeks) to 5 years with a total of 4,081 patients.

Table 2: Adverse Drug Reactions Reported in Other Clinical Trials Involving Travoprost Ophthalmic Solution, 0.004%

System Organ Classification	Preferred Term*	
Immune system disorders	Uncommon:	hypersensitivity
Nervous system disorders	Rare:	dysgeusia
Eye disorders	Common:	iris hyperpigmentation, ocular discomfort.
	Uncommon:	cataract, corneal erosion, eyelids pruritus, keratitis, lacrimation increased, periorbital oedema, visual acuity reduced
	Rare:	anterior chamber pigmentation, asthenopia, conjunctival follicles, conjunctival oedema, eczema eyelids, eye allergy, eyelash discolouration, eye inflammation, eyelid irritation, hypoaesthesia eye, iridocyclitis, uveitis
Cardiac disorders	Rare:	heart rate decreased, palpitations
Vascular disorders	Rare:	hypertension
Respiratory, thoracic and mediastinal disorders	Rare:	asthma, cough, dyspnoea, nasal discomfort, nasal dryness, oropharyngeal pain
Gastrointestinal disorders	Rare:	constipation, dry mouth
Skin and subcutaneous tissue disorders	Uncommon :	skin hyperpigmentation
	Rare:	hair colour changes, hypertrichosis, madarosis
General disorders and administration site conditions	Rare	asthenia

* Within each frequency-grouping, ADRs are presented in alphabetical order.

Additional ADRs identified from post-marketing surveillance of travoprost ophthalmic solution, 0.004% are listed below in alphabetical order. The frequencies of these events cannot be determined from the available data:

Abdominal pain, anxiety, arthralgia, chest pain, depression, diarrhea, dysuria, erythema, hypotension, macular oedema, musculoskeletal pain, nausea, prostatic specific antigen increased, sunken eyes, tinnitus, urinary incontinence.

DRUG INTERACTIONS

Overview

Drug interaction studies with cytochrome P450 substrates have not been conducted with AL-5848 (travoprost active acid metabolite). The very low systemic exposure to AL-5848 after topical ocular administration of travoprost would not likely influence the P450 enzyme-mediated metabolism of other concomitant agents. Concomitant administration of potent inhibitors of

cytochrome P450 enzymes would not impact the low systemic exposure of AL-5848 after topical ocular administration since travoprost is metabolized extensively by routes other than the cytochrome P450 pathways.

Drug-Drug Interactions
Drug-drug interactions with other concomitantly administered drugs are not likely to be clinically relevant. As reported, plasma levels following topical ocular administration of Travoprost 0.004% are very low (approximately 70% below the assay LOQ of 10 pg/mL) and those that were measurable declined rapidly ($t_{1/2}$ approximately 45 minutes).

Drug-Food Interactions
Interactions with food have not been established.

Drug-Herb Interactions
Interactions with herbal products have not been established.

Drug-Laboratory Interactions
Interactions with laboratory tests have not been established.

Drug-Lifestyle Interactions
Interactions with functions of daily living have not been established.

DOSAGE AND ADMINISTRATION

Recommended Dose and Dosage Adjustment
The recommended dosage for APO-TRAVOPROST is one drop in the affected eye(s) once daily. Optimal effect is observed with evening dosing. APO-TRAVOPROST should not be administered more than once daily since it has been shown that more frequent administration of prostaglandin analogs may decrease the intraocular pressure lowering effect.

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

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.

Administration
For ophthalmic use only.

Travoprost may be used concomitantly with other topical ophthalmic products including beta-blockers (i.e., timolol) and brinzolamide 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.

OVERDOSAGE

There have been no reported cases of overdose for travoprost ophthalmic solution, 0.003% during the clinical development program.

A topical overdose of travoprost ophthalmic solution, 0.003% may be flushed from the eye(s) with lukewarm water. Treatment of a suspected oral ingestion is symptomatic and supportive.

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

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.

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 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.

APO-TRAVOPROST, 0.003%, when applied topically to the eye, reduces elevated as well as normal intraocular pressure, whether or not accompanied by glaucoma. Elevated intraocular pressure is a major risk factor in the pathogenesis of glaucomatous visual field loss. The higher the level of intraocular pressure, the greater the likelihood of glaucomatous visual field loss and optic nerve damage. The Advanced Glaucoma Intervention Study (AGIS) established elevated intraocular pressure 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.

Pharmacodynamics

Since travoprost ophthalmic solution, 0.003% is a topical product intended for a local effect within the eye, plasma drug concentrations cannot be related to pharmacodynamics (IOP-lowering).

Pharmacokinetics

There have been no studies conducted to evaluate the pharmacokinetics of travoprost ophthalmic solution, 0.003% in humans. The absorption, distribution, metabolism, excretion and toxicokinetics of AL-6221 have been studied in travoprost ophthalmic solution 0.004% BAK-preserved and BAK-free formulations. Clinical pharmacokinetic studies in normal subjects, Japanese normal subjects, renally-impaired and hepatically-impaired subjects with travoprost ophthalmic solution 0.004% showed extremely low systemic exposure with most plasma samples containing travoprost free acid concentrations below the 0.010 ng/mL limit of quantitation. For those samples containing quantifiable drug levels, concentrations ranged from 0.010 to 0.052 ng/mL. In the few subjects having sufficient quantifiable data for half-life determination, the elimination half-life was approximately 45 minutes. There was insufficient

quantifiable data for calculation of AUC, clearance or volume of distribution. Data in animals indicates that travoprost exhibits linear pharmacokinetics. Since travoprost ophthalmic solution, 0.003% contains a 25% lower dose than the 0.004% solution used in clinical pharmacokinetic studies, systemic exposure would be even lower than that observed previously indicating that the systemic pharmacokinetics travoprost and its active free acid metabolite are not a cause of concern for the safety of travoprost ophthalmic solution, 0.003%.

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 to 6 ng equiv./g). Binding of travoprost free acid to plasma proteins is moderate at 90% and linear over a 10,000-fold concentration range (0.10 to 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. Bio-transformations 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. Approximately 75% of the dose was eliminated in the feces with the remainder excreted in urine.

Special Populations and Conditions

Pediatrics: The efficacy and safety of travoprost ophthalmic solution, 0.003% in pediatric patients have not been established, and use is not recommended in these patients until further data become available.

Geriatrics: There were no differences seen between elderly patients and younger patients with travoprost ophthalmic solution, 0.003%. Additionally, no differences were seen in the efficacy and safety of travoprost ophthalmic solution, 0.003% compared to travoprost ophthalmic solution, 0.004% BAK formulation in elderly patients.

Gender: No meaningful differences in AL-5848 pharmacokinetics were observed between male and female subjects indicating no gender differences in the pharmacokinetics of travoprost free acid (AL-5848).

Hepatic Insufficiency: After administration of travoprost ophthalmic solution, 0.004% (BAK-preserved) formulation, once daily for 7 days, the systemic exposure of AL-5848 is minimal and levels cannot be correlated with the severity of hepatic impairment. No dose adjustment of travoprost 0.004% BAK formulation is necessary in patients with different degrees (mild to severe) of hepatic impairment. Based on these results, no dose adjustment of travoprost ophthalmic solution, 0.003% is necessary.

Race: A single-centre, open-label, randomized, 3 parallel-group, multiple-dose safety pharmacokinetic study in healthy male Japanese subjects was conducted to characterize the steady-state plasma pharmacokinetics of travoprost and AL-5848. Thirty-eight subjects (19 to 64 years of age) received topical ocular administration of either travoprost 0.004 (with or without digital punctal occlusion) or travoprost 0.0015% without digital punctal occlusion once-daily in the morning for 7 days (one drop in each eye). The results demonstrated that the systemic exposure of travoprost and AL-5848 was minimal in healthy male Japanese volunteers after repeated topical ocular administration of travoprost 0.004% or travoprost 0.0015%. Punctal occlusion did not influence the systemic availability of AL-5848.

Renal Insufficiency: Plasma concentrations of travoprost and its active metabolite (AL-5848) observed were similar to those reported in healthy subjects and in patients with varying degrees of hepatic impairment. The majority of post-dose plasma samples were below the assay LOQ (<10 pg/mL). No dose adjustment of travoprost 0.004% BAK formulation was necessary in patients with different degrees (from mild to severe) of renal impairment. Based on these results, no dose adjustment of travoprost ophthalmic solution, 0.003% is necessary.

STORAGE AND STABILITY

Store at 2°C to 25°C. Refrigeration is not required.

Protect from light. Keep bottle in outer cardboard packaging when not in use.

Do not use APO-TRAVOPROST for more than 125 days after opening the 5 mL bottle.

Keep out of the reach and sight of children.

SPECIAL HANDLING INSTRUCTIONS

This medicinal product does not require any special storage conditions.

DOSAGE FORMS, COMPOSITION AND PACKAGING

APO-TRAVOPROST is a sterile, isotonic, buffered, preserved, aqueous solution containing 30 mcg/mL travoprost supplied in a plastic bottle.

APO-TRAVOPROST is supplied as a 5 mL solution in a plastic bottle. The dispenser bottles are made of polypropylene and fitted with a translucent polypylene dropper tip and a turquoise polypropylene overcap. Tamper evidence is provided with a safety seal on the outer carton.

Each mL of solution contains:

ACTIVE:	travoprost 0.03 mg/mL
PRESERVATIVE:	Polyquantemium-1 0.01 mg/mL
INACTIVES:	boric acid, mannitol, polyoxyl 40 hydrogenated castor oil, propylene glycol, sodium chloride, hydrochloric acid and/or sodium hydroxide (to adjust pH), and water for injection.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: Travoprost USP

Chemical name: 5Z)-isopropyl-7-((1*R*,2*R*,3*R*,5*S*)-2-((*R,E*)-4-(3-trifluoromethyl) phenoxy)-3-hydroxybut-1-enyl)-3,5-dihydroxycyclopentyl)hept-5-enoate

USP:

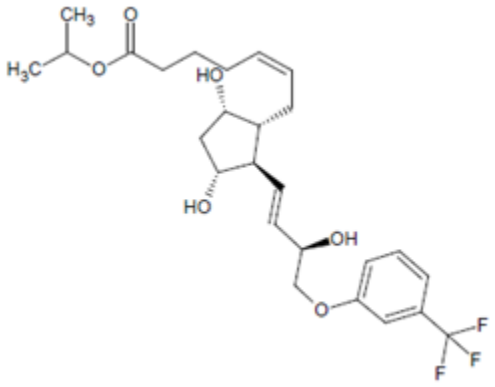
1) [1*R*-[1α(*Z*),2β(1*E*,3*R**),3α,5α]]-7-[3,5-Dihydroxy-2-[3-hydroxy-4-[3-(trifluoromethyl)phenoxy]-1-butenyl]cyclopentyl]-5-heptenoic acid, 1-methylethylester

2) 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

Molecular formula: $C_{26}H_{35}F_3O_6$

Molecular weight: 500.55 g/mol

Structural formula:



Physicochemical properties: Travoprost is a pale yellow to yellowish viscous oil. Freely soluble in Acetonitrile, Toluene, Ethyl Acetate and Methanol; practically insoluble in Water and Hexane.

pH: Travoprost has such low solubility in water; it is not possible to prepare aqueous solution that would give a meaningful pH value.

CLINICAL TRIALS

In three controlled clinical studies, with durations from 6 to 12 months (C-97-71, C-97-72 and C-97-79), patients with open-angle glaucoma or ocular hypertension were treated once daily in the evening with travoprost ophthalmic solution, 0.004% (BAK- preserved). Travoprost ophthalmic solution, 0.004% demonstrated 6.7 to 9.0 mmHg reduction in IOP. Stable diurnal IOP reductions were achieved as early as 2 weeks after initiation of therapy and were maintained over the 6 to12 month treatment period.

In a multicentre, randomized, double-masked trial (C-97-73), patients with mean baseline IOP of 24 to 26 mmHg on timolol maleate ophthalmic solution 0.5% BID, who were treated with travoprost ophthalmic solution, 0.004% (BAK- preserved) dosed QD adjunctively to timolol maleate ophthalmic solution 0.5% BID, demonstrated 6 to 7 mmHg additional reductions in IOP.

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

Table 3 summarizes the demographic characteristics of the population included in the clinical trials described above, and Table 4 summarizes the efficacy results of these studies.

Table 3: Summary of Patient Demographics for Clinical Trials Related to Specific Indication

Study #	Trial Design	Dosage, Route of Administration and Duration	Study Subjects (N)	Mean Age (Range)	Gender (M/F)
C-97-71	Randomized, triple masked, multi-centre, parallel group, active control in patients with open-angle glaucoma or ocular hypertension	1 drop QD of placebo (8AM) + 1 drop QD (8PM) travoprost 0.004% or 0.0015%; 1 drop QD of placebo (8AM) + 1 drop QD (PM) latanoprost 0.005%; 1 drop BID of timolol maleate ophthalmic solution 0.5% (8AM and 8PM). 12 months.	787	64.2 years (22 - 94)	392 M 395 F
C-97-72	Randomized, triple masked, multi-centre, parallel group, active control in patients with open-angle glaucoma or ocular hypertension	1 drop QD of placebo (8AM) + 1 drop QD (8PM) travoprost 0.004% or 0.0015%; 1 drop of timolol maleate ophthalmic solution 0.5% (8AM and 8PM); 6 months.	594	63.7 years (21 - 91)	293 M 301 F
C-97-73	Randomized, multi-centre, 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 maleate ophthalmic solution 0.5% dosed BID.	1 drop QD (8PM) of travoprost 0.004% or 0.0015% + 1 drop BID of open-label timolol maleate ophthalmic solution 0.5% (8AM and 8PM); 1 drop QD (8PM) of placebo plus 1 drop BID of open-label timolol maleate ophthalmic solution 0.5% (8AM and 8PM). 6 months.	410	63.7 years (11 - 89)	180 M 230 F
C-97-79	Randomized, multi-centre, triple masked, active controlled, parallel group study in patients with open angle glaucoma or ocular hypertension	1 drop QD of placebo (9AM) + 1 drop QD (9PM) travoprost 0.004% or 0.0015%; 1 drop BID of timolol maleate ophthalmic solution 0.5% (9AM and 9PM) 9 months.	572	63.3 years (31 - 88)	284 M 288 F
C-01-74	Randomized, double-masked, multi-centre, parallel group, active-controlled in patients with open-angle glaucoma or ocular hypertension	1 drop QD of placebo (9 AM) + 1 drop QD (9PM) travoprost 0.004%; 1 drop QD of latanoprost/timolol 0.5% (9AM) + 1 drop QD of placebo (9PM). 6 weeks.	106	68.0 years (34 - 86)	46 M 60 F

QD = once daily

Table 4: Mean Baseline IOP and Mean Change from Baseline IOP Measurements[1]

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, 0.004%	26.8	25.2	24.6	-7.6	-7.4	-6.9
Timolol	26.9	25.3	24.6	-6.7	-6.1	-5.3
Latanoprost	26.9	25.2	24.9	-7.7	-6.9	-6.3
C-97-72						
Travoprost ophthalmic solution, 0.004%	27.3	25.7	25.1	-7.6	-7.2	-7.0
Timolol	27.4	25.8	25.4	-6.8	-6.0	-5.1
C-97-73						
Travoprost ophthalmic solution, 0.004% / timolol	26.0	24.5	24.6	-6.8	-6.4	-6.0
Timolol	26.4	24.8	24.4	-2.6	-1.8	-1.6
C-97-79[a]						
Travoprost ophthalmic solution, 0.004%	27.4	26.5	25.6	-8.8	-8.7	-8.2
Timolol	27.0	26.2	25.1	-7.7	-7.5	-6.6
C-01-74[b]						
Travoprost ophthalmic solution, 0.004%	25.3	--	24.3	-6.9	--	-6.8
latanoprost / timolol	24.6	--	23.9	-6.4	--	-6.1

[1] Least squares means from repeated measures ANOVA model
[a] C-97-79 IOP measurements were taken at 9 AM, 11 AM and 4 PM.
[b] C-01-74 IOP measurements were taken at 9 AM and 5 PM. No statistical comparisons of treatments were carried out.

Study C-11-034 was designed to demonstrate equivalence of travoprost ophthalmic solution, 0.003% (polyquaternium-1 preserved) to travoprost ophthalmic solution, 0.004% (BAK-preserved), with both dosed once daily in the evening in patients with open-angle glaucoma or ocular hypertension. Overall, 864 patients were enrolled and randomized to 1 of 2 treatment groups: travoprost ophthalmic solution, 0.003% (polyquaternium-1 preserved) or travoprost ophthalmic solution, 0.004% (BAK-preserved). Of the 864 patients enrolled, 860 patients were evaluable for intent to treat analysis, 851 patients were evaluable for per protocol analysis and 863 were evaluable for safety (Table 5).

Table 5: Summary of Patient Demographics for Study C-11-034 in Patients with Open-Angle Glaucoma or Ocular Hypertension

Study #	Trial Design	Dosage, Route of Administration and Duration	Study Subjects (n)	Mean Age (Range) for Safety Dataset	Gender (M/F)
C-11-034 (pivotal study)	Multicentre, double-masked, randomized, active-controlled, 2-arm, parallel-group, equivalence study	Travoprost 0.003% Solution 1 drop QD 8 PM Topical ocular	442	65.2 years	Male = 348 Female = 515
		Travoprost 0.004% BAK, 1 drop QD 8 PM Topical ocular	422		

Primary and Supportive Efficacy Endpoints for Study C-11-034

The primary efficacy parameter was IOP at Week 2, Week 6 and Month 3 for each assessment time point (8 AM, 10 AM and 4 PM).

Supportive efficacy included:

- IOP change from baseline and IOP percent change from baseline at each visit (Week 2, Week 6 and Month 3) and assessment time point (8 AM, 10 AM and 4 PM),
- the percentage of patients who achieved a target IOP level <18 mmHg at each visit and assessment time point, and
- the percentage of patients who achieved IOP lowering of at least 30% from baseline at each visit and assessment time point.

Study Results

Primary Efficacy Results

The IOP-lowering efficacy of travoprost ophthalmic solution, 0.003% was equivalent to travoprost ophthalmic solution, 0.004% at all on-therapy study visits and assessment time points. In the primary efficacy analysis, in order to conclude equivalence, the 2-sided 95% CI for the difference in IOP between treatment groups must have been within ± 1.5 mmHg at each of the 3 assessment time points (8 AM, 10 AM, and 4 PM) for each on-therapy visit (Week 2, Week 6 and Month 3). The least squares mean treatment group differences ranged from -0.3 to 0.0 mmHg with CIs ranging from -0.7 to 0.4 mmHg (Table 6). Thus, equivalence was met since all 9 of the assessments had CIs that were entirely within the pre-specified ± 1.5 mmHg margins. Further, all 9 of the assessments had CIs that were entirely within a ± 1.0 mmHg margin.

Table 6: Comparison of Mean IOP (mmHg) at Week 2, Week 6, and Month 3 (C-11-034 – Intent-to-Treat Data)

Visit	Travoprost Ophthalmic Solution, 0.003%			Travoprost Ophthalmic Solution, 0.004%			
	Time Point	N	Mean (SE)	N	Mean (SE)	Mean Difference[a]	(95% CI)
Week 2	8 AM	442	19.4 (0.16)	416	19.5 (0.17)	-0.1	(-0.5, 0.3)
	10 AM	442	18.6 (0.16)	416	18.6 (0.16)	-0.0	(-0.4, 0.4)
	4 PM	442	18.0 (0.16)	416	18.3 (0.16)	-0.3	(-0.7, 0.1)
Week 6	8 AM	439	19.3 (0.16)	413	19.3 (0.17)	-0.0	(-0.4, 0.4)
	10 AM	440	18.5 (0.16)	413	18.6 (0.17)	-0.1	(-0.5, 0.3)
	4 PM	440	18.0 (0.16)	413	18.1 (0.17)	-0.2	(-0.6, 0.2)
Month 3	8 AM	432	19.2 (0.17)	408	19.3 (0.18)	-0.1	(-0.5, 0.3)
	10 AM	432	18.3 (0.17)	408	18.6 (0.18)	-0.3	(-0.7, 0.1)
	4 PM	431	18.0 (0.16)	408	18.0 (0.17)	0.0	(-0.4, 0.4)

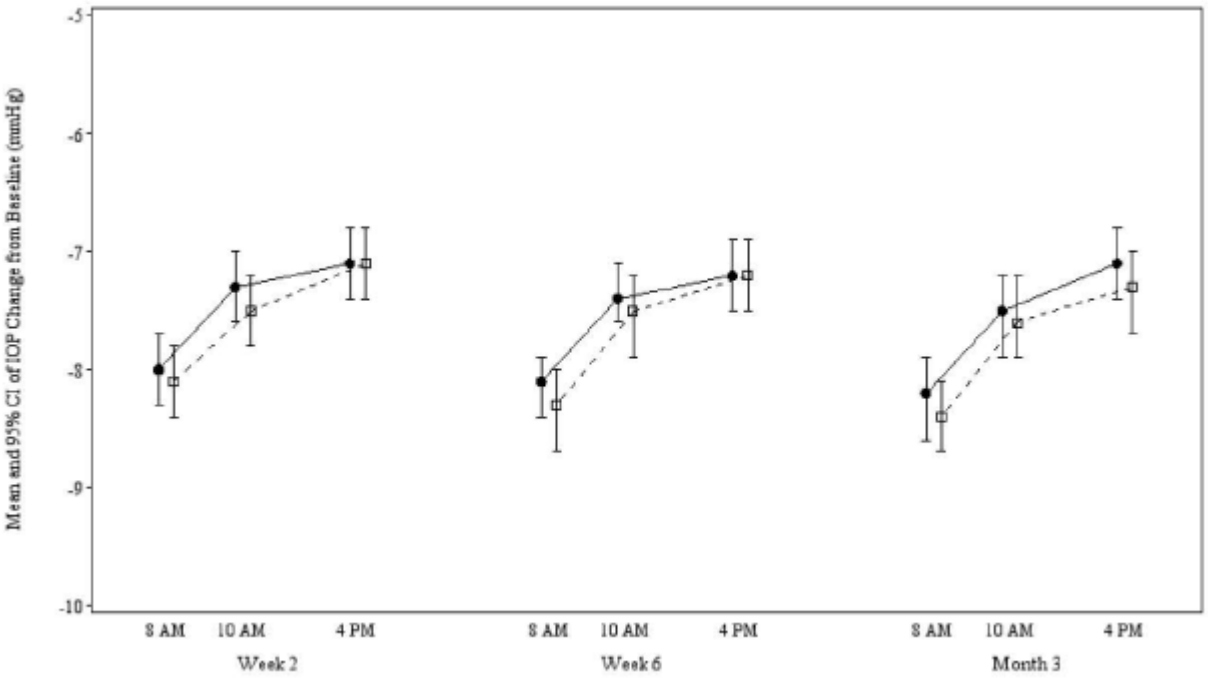
Travoprost ophthalmic solution, 0.003% = Travoprost 30 mcg/mL eye drops, solution preserved with polyquaternium-1
Travoprost ophthalmic solution, 0.004% = Travoprost 40 mcg/mL eye drops, solution preserved with BAK
SE = Standard Error; CI = Confidence Interval
[a] Estimates based on least squares means derived from a statistical model that accounts for correlated IOP measurements within patient where site and actual 8 AM baseline IOP stratum are in the model.

Supportive Efficacy Results

For each supportive efficacy endpoint, analysis provided no evidence of difference in IOP-lowering efficacy between travoprost ophthalmic solution, 0.003% and travoprost ophthalmic solution, 0.004%.

The mean changes and percent changes in IOP from baseline to each study visit and assessment time point revealed no marked differences between treatment groups. The mean reductions in IOP within the travoprost ophthalmic solution, 0.003%group ranged from 7.1 to 8.2 mmHg; the mean reductions in IOP within the travoprost ophthalmic solution, 0.004% group ranged from 7.1 to 8.4 mmHg (Figure 1). The percent reductions in IOP from baseline to each study visit and assessment time point ranged from 28.4% to 30.7% (Table 7). The percent reductions in IOP were similar across treatment groups at each individual assessment time point, and did not vary markedly from Week 2 to Week 6 or Month 3 in either treatment group. These results are consistent with and supportive of the primary efficacy conclusion that the two study drugs are equivalent.

Figure 1: Means and 95% Confidence Intervals for IOP Changes from Baseline (mmHg) by Visit (Intent-to-Treat Data)



••• Travoprost 0.003% □□□ Travoprost Ophthalmic Solution 0.004%

Table 7: Descriptive Statistics for IOP Percent Change from Baseline (mmHg) by Visit (Intent-to-Treat Data)

		Travoprost Ophthalmic Solution, 0.003%			Travoprost Ophthalmic Solution, 0.004%		
Visit		**8 AM**	**10 AM**	**4 PM**	**8 AM**	**10 AM**	**4 PM**
Week 2	**N**	442	442	442	416	416	416
	Mean	-29.7	-28.4	-28.7	-29.9	-29.3	-28.5
	SD	10.67	10.97	11.43	11.33	11.44	11.55
	(Min, Max)	(-58, 0)	(-61, 11)	(-59, 9)	(-60, 4)	(-63, 9)	(-59, 5)
	95% CI	(-30.7, -28.7)	(-29.4, -27.4)	(-29.7, -27.6)	(-31.0, -28.8)	(-30.4, -28.3)	(-29.6, -27.4)
Week 6	**N**	439	440	440	413	413	413
	Mean	-30.3	-28.9	-28.8	-30.8	-29.4	-29.1
	SD	10.78	10.89	11.35	11.36	11.36	11.11
	(Min, Max)	(-61, 14)	(-62, 8)	(-63, 4)	(-65, 8)	(-59, 14)	(-57, 8)
	95% CI	(-31.3, -29.3)	(-30.0, -27.9)	(-29.9, -27.7)	(-31.9, -29.7)	(-30.5, -28.3)	(-30.2, -28.0)
Month 3	**N**	432	432	431	408	408	408
	Mean	-30.7	-29.5	-28.5	-31.0	-29.5	-29.4
	SD	11.29	11.44	11.48	10.93	11.50	11.37
	(Min, Max)	(-61, 30)	(-59, 8)	(-63, 9)	(-60, 11)	(-64, 25)	(-64, 17)
	95% CI	(-31.7, -29.6)	(-30.6, -28.5)	(-29.6, -27.4)	(-32.1, -30.0)	(-30.6, -28.4)	(-30.5, -28.3)

Travoprost ophthalmic solution, 0.003% = Travoprost 30 mcg/mL eye drops, solution preserved with polyquaternium-1
Travoprost ophthalmic solution, 0.004% = Travoprost 40 mcg/mL eye drops, solution preserved with BAK

No marked differences between treatment groups were noted based upon the number and percentage of patients with IOP measurements less than 18 mmHg (Table 8). Approximately 33% to 55% of the patients had an IOP measurement below 18 mmHg during the study. While the percentages of patients whose IOP measurements were below this threshold varied across study visits and assessment time points, no marked differences were noted between treatment groups at any specific assessment. In both groups, the relevant percentages increased throughout the day, but did not vary substantially from Week 2 to Month 3.

Table 8: Number and Percentage of Patients with IOP <18 mmHg by Visit and Time Point (Intent-to-Treat Data)

	Travoprost Ophthalmic Solution, 0.003%						**Travoprost Ophthalmic Solution, 0.004%**					
	8 AM		**10 AM**		**4 PM**		**8 AM**		**10 AM**		**4 PM**	
	Total	**N (%)**	**Total**	**N (%)**	**Total**	**N (%)**	**Total**	**N (%)**	**Total**	**N (%)**	**Total**	**N (%)**
Week 2	**442**	147 (33.3)	**442**	208 (47.1)	**442**	237 (53.6)	**416**	153 (36.8)	**416**	187 (45.0)	**416**	216 (51.9)
Week 6	**439**	172 (39.2)	**440**	195 (44.3)	**440**	240 (54.5)	**413**	156 (37.8)	**413**	181 (43.8)	**413**	218 (52.8)
Month 3	**432**	167 (38.7)	**432**	211 (48.8)	**431**	231 (53.6)	**408**	154 (37.7)	**408**	191 (46.8)	**408**	214 (52.5)

Travoprost ophthalmic solution, 0.003% = Travoprost 30 mcg/mL eye drops, solution preserved with polyquaternium-1
Travoprost ophthalmic solution, 0.004% = Travoprost 40 mcg/mL eye drops, solution preserved with BAK

No marked differences between treatment groups were noted based on the number and percentage of patients with IOP-lowering of at least 30% relative to baseline (Table 9). No marked differences were noted between treatment groups when compared at an individual study visit and assessment time point. The greatest observed percentages were 53.7% in the travoprost ophthalmic solution, 0.003% group (also at 8 AM on Month 3). Overall, at every study visit and assessment time point, at least 43.9% of the patients in the travoprost ophthalmic solution, 0.003% group and 44.2% of the patients in the travoprost ophthalmic solution, 0.004% group had a reduction in IOPs of at least 30% relative to baseline.

Table 9: Number and Percentage of Patients with IOP Lowering of at Least 30% from Baseline by Visit and Time Point (Intent-to-Treat Data)

	Travoprost Ophthalmic Solution, 0.003%						Travoprost Ophthalmic Solution, 0.004%					
	8 AM		10 AM		4 PM		8 AM		10 AM		4 PM	
	Total	N (%)	Total	N (%)	Total	N (%)	Total	N (%)	Total	N (%)	Total	N (%)
Week 2	**442**	219 (49.5)	**442**	194 (43.9)	**442**	208 (47.1)	**416**	197 (47.4)	**416**	201 (48.3)	**416**	(44.2)
Week 6	**439**	232 (52.8)	**440**	200 (45.5)	**440**	196 (44.5)	**413**	216 (52.3)	**413**	206 (49.9)	**413**	(47.5)
Month 3	**432**	232 (53.7)	**432**	228 (52.8)	**431**	192 (44.5)	**408**	222 (54.4)	**408**	204 (50.0)	**408**	(48.3)

Travoprost ophthalmic solution, 0.003% = Travoprost 30 mcg/mL eye drops, solution preserved with polyquaternium-1
Travoprost ophthalmic solution, 0.004% = Travoprost 40 mcg/mL eye drops, solution preserved with BAK

DETAILED PHARMACOLOGY

That pharmacology, safety pharmacology, pharmacokinetic and toxicological attributes of travoprost in non-clinical models has been extensively characterized. The non-clinical assessment of travoprost is based upon the already established non-clinical profiles of the active drug substance relative to ocular safety, local tolerance and potential systemic exposure.

Human Data

Pharmacodynamics

In Vitro Studies
In vitro protein binding of AL-5848, the active metabolite of travoprost, has been studied in human plasma. Binding of AL-5848 to plasma proteins was moderate (80%) over a 10,000-fold concentration range.

Pharmacokinetics

Phase I trials with travoprost 0.004% (BAK-preserved) or timolol 0.5% ophthalmic solutions were conducted to fully characterize the steady-state plasma pharmacokinetics of travoprost and AL-5848 in healthy subjects (C-99-08) and male Japanese (C-00-15) subjects, as well as in patients with renal (C-99-97) or hepatic (C-005-05) impairment. Studies C-99-08 and C-00-15 involved once-daily topical ocular administration of either travoprost 0.004% (BAK-preserved) or travoprost 0.0015% ophthalmic solutions for both eyes for 7 days. The renal (C-99-97) and hepatic (C-00-05) impairment studies involved once-daily bilateral administration of travoprost ophthalmic solution, 0.004% (BAK-preserved) for 7 days. One controlled study (C-02-35) was conducted to determine plasma pharmacokinetics of AL-5848 and timolol, when the travoprost/timolol ophthalmic solution was administered compared to when travoprost 0.004% (BAK-preserved) and timolol 0.5% ophthalmic solutions were administered independently,

following a once-daily dosing regimen for 3 days.

A summary of plasma pharmacokinetic parameters of the travoprost active acid metabolite (AL-5848) across Phase I studies is presented below (Table 10).

Table 10: Plasma Pharmacokinetics of AL-5848 across Phase I Studies Following Topical Ocular Dosing with Travoprost Ophthalmic Solution, 0.004% BAK-preserved)

Study	Treatment	C_{max} (pg/mL)	T_{max} (hr)	$T_{1/2}$ (hr)	N
C-99-08	Travoprost, 0.004% (BAK-preserved)	15 ± 5	0.26 ± 0.12	ND	16
C-00-05	Travoprost, 0.004% (BAK-preserved)	21 ± 8	0.27 ± 0.16	0.75 ± 0.23[a]	31
C-99-97	Travoprost, 0.004% (BAK-preserved)	14 ± 3	0.19 ± 0.04	ND	4
C-00-15	Travoprost, 0.004% (BAK-preserved)	15 ± 6	0.18 ± 0.06	ND	7
C-02-35	Travoprost, 0.004% (BAK-preserved)	16 ± 4	0.42 ± 0.14	ND	3

Values represent means ± standard deviation
N Number of pharmacokinetic profiles with at least one quantifiable assay value.
ND Not determined because of insufficient data for calculation.
[a] Mean $t_{1/2}$ based on values from 22 subjects.

In approximately two-thirds of subjects administered travoprost ophthalmic solution, 0.004% (BAK-preserved) across the 5 studies, no quantifiable AL-5848 concentrations were measured. In about 70% of the profiles, plasma concentrations were below the assay Limit Of Quantification (LOQ) (< 10 pg/mL). In those pharmacokinetic profiles with quantifiable concentrations of AL-5848, the mean C_{max} for travoprost acid metabolite (AL-5848) was comparable across the 5 studies (ranging from 15 to 21 pg/mL). In all but one subject for whom quantifiable plasma concentrations of AL-5848 were observed, the C_{max} was observed within 30 minutes after dosing. One subject in Study C-00-05 had a T_{max} value of 45 minutes. A total of 22 pharmacokinetic profiles, representing 14 subjects, had sufficient quantifiable concentrations of AL-5848 to estimate a $t_{1/2}$ which had a mean value of 45 ± 14 minutes (0.75 ± 0.23 hours). The elimination of AL-5848 from plasma was rapid, resulting in residual levels that were generally below the assay LOQ (10 pg/mL) within one hour post-dose.

Single- and multiple-dose pharmacokinetics of travoprost were assessed in a total of 5 Phase I studies. The plasma concentrations of AL-5848 were similar after the single- and multiple-dose administration across all 5 studies.

A comparison of pharmacokinetic results for AL-5848 after the first dose and the last dose (steady-state) of travoprost ophthalmic solution, 0.004% (BAK-preserved) in healthy subjects and Japanese subjects, and in patients with renal or hepatic impairment, dosed once-daily for 7 days, showed a similar pattern of low systemic exposure across these 4 studies (C-99-08, C-99-97, C-00-05, C-00-15). The majority of plasma concentrations were below the assay LOQ (10 pg/mL). Furthermore, there was no evidence of drug accumulation after repeated

administration of travoprost ophthalmic solution, 0.004% (BAK-preserved) across studies, including those studies of patients with renal and hepatic impairment.

The low systemic concentrations of AL-4858 observed in Study C-02-35 after repeated ocular administration (3 days) of Travoprost 0.004% BAK or travoprost/timolol ophthalmic solution were also consistent with those observed in healthy subjects (C-99-08) and Japanese (C-00-15) subjects and patients with renal (C-99-97) or hepatic (C-00-05) impairment. There were no apparent differences in the concentrations of AL-5848 between Day 1 and Day 3, indicating no accumulation of drug, and there were no observable differences between treatments.

Animal Data

Pharmacodynamics

In Vivo Studies
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.

Table 11: Reduction of IOP following BID Travoprost (AL-6221) in Lasered Cynomolgus Monkeys

Dose (mcg)	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[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; TN = Tears Naturale
[2] BID 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 for one week. Systemic circulatory parameters were not affected by drug treatment.

In a safety study in naïve dark-adapted Dutch-belted rabbits, a single subcutaneous dose of vehicle (1.6 mL/kg) or 100 mcg/kg of travoprost produced no significant changes in the peak amplitudes or latencies of the A-wave or the B-wave of the flash electroretinogram (ERG) measured at 1 hour or 1 week after dosing. This suggests that travoprost produces no functional changes in the photoreceptors or the inner retinal layers of the eye at a dose approximately 2,000 times higher than the maximum recommended clinical dose of 0.046 mcg/kg/day.

In Vitro Studies

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 les potent in binding to other receptors. Travoprost demonstrates higher potency and higher selectivity for the FP receptor compared to latanoprost.

Table 12: 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 phophoinositide (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 the system.

Table 13: Second Messenger Study: Potency & Efficacy

	FP PI Turnover	DP Cyclase Stim	EP2 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 of over 32 different non-prostanoid receptors, including muscarinic, alpha-adrenergic, beta-adrenergic, and endothelin receptors at concentrations up to 10 mcM.

Safety Pharmacology

Major findings from safety pharmacology studies with travoprost (AL-6221) or its free acid, AL-5848, were consistent with known pharmacology of PFG_{α} and its analogues, a small to moderate increase in cardiac contractility in dogs, a dose-related increase in GI propulsion in mice, and contractions in estrogen-primed rat uterus. The increases in cardiac contractility and increase in GI propulsion were observed at doses that were approximately 28 to 833 times the recommended clinical dose (0.036 mcg/kg/day) of travoprost ophthalmic solution, 0.003%. While the lowest concentration that produced a measureable increase in contractions in isolated uterus strips was about 6-fold higher than the highest concentration measured in humans after a dose of 0.048 mcg/kg/day. Additionally, the concentration of travoprost that can actually reach the uterus after the therapeutic use of travoprost ophthalmic solution, 0.003% will be substantially lower than the concentration of travoprost bathing isolated rat uterus strips in this study.

Based on the results of the safety pharmacology studies, and the established safety of travoprost ophthalmic solution, 0.004% (BAK-preserved) and travoprost ophthalmic solution, 0.004% Z (ionic buffered system-preserved), the safety margin for travoprost ophthalmic solution, 0.003% administered by topical ocular route is considered sufficiently wide to preclude any concerns of significant functional adverse events in humans.

Pharmacokinetics

Following topical ocular administration of travoprost ophthalmic solution, 0.004% (BAK-preserved) to rabbits, AL-6221 was rapidly absorbed into the eye and its isopropyl ester hydrolyzed to the pharmacologically active metabolite AL-5848. As a result, AL-5848 levels are substantially higher than AL-6221 levels. In the rabbit cornea and aqueous humor, the maximal concentrations of AL-5848 were 405 ng/g and 20.2 ng/g versus 32.9 ng/g and 0.820 ng/g for AL-6221, respectively. AL-5848 concentrations declined with half-lives of 1.2 to 1.4 hours in these tissues.

Studies in pigmented rabbits demonstrated that both AL-6221 and AL-5848 do not have a binding affinity for melanin pigmented ocular tissues.

Travoprost exhibits low oral bioavailability (< 3 to 6%). As a result, the pharmacokinetics of AL-5848 following subcutaneous doses of AL-6221 were determined in order to demonstrate the suitability of this route for use in Toxicology studies. The results of these studies demonstrated dose proportionality (C_{max} and AUC) and rapid distribution from the site (T_{max} 20 to 40 minutes). The percent of dose absorbed from the subcutaneous depot was demonstrated to be high from radioactivity studies where approximately 96% of the dose was absorbed by 72 hours after dosing. These results demonstrated that the subcutaneous route provides suitable exposure in toxicology studies.

In rats, radioactivity distributes widely in the body following subcutaneous doses of ^{3}H-AL-6221. Tissue concentrations after 14-daily 0.1 mg/kg doses were higher than after a single dose by approximately 3.5-fold. Radioactivity concentrations declined rapidly and after a single dose were below detection limits in most tissues by 24 hours. In contrast, after a multiple dose regimen, radioactivity concentrations were measurable to 168 hours. Highest concentrations of radioactivity were found in kidney, liver, lung and plasma which were typically 10-fold higher than in other tissues. Tissues with low levels of radioactivity included brain, testes, muscle and fat which had maximal levels approximately 50-fold lower than in kidney, liver, lung and plasma.

Tissue concentrations declined rapidly with a profile similar to that in plasma. After C_{max}, concentrations declined in a biphasic manner. During the initial rapid decline, greater than 90% of radioactivity in most tissues was eliminated.

The percent of ^{3}H-AL-5848 bound to human, monkey and rat plasma proteins was concentration independent over a wide range (0.01 to 100 ng/mL), similar between species and moderate at approximately 80%. As a result, drug-drug interactions involving protein binding are unlikely.

The metabolism of AL-6221/AL-5848 follows that of endogenous prostaglandins such as prostaglandin PG-F2$_{\alpha}$. The first step in this metabolic pathway involves oxidation of the 15-hydroxyl by cytosolic NAD+/NADP+ dependent prostaglandin 15-hydroxyl dehydrogenase. This is followed by reduction of the 13, 14-double bond by a NADPH dependent 15-keto prostaglandin reductase, also a cytosolic enzyme. Cleavages of the carboxylic side chain then proceeds via mitochondrial beta- and endoplasmic reticulum gamma-oxidases.

Studies in rats showed that radioactivity from ^{3}H-AL-6221 doses is rapidly excreted in urine and feces. Ninety-five percent of the dose was recovered in the excreta in the first 24 hours. After 168 hours, only about 0.3% remained in the carcass. The major route of excretion is by biliary excretion and fecal elimination (74%).

Radioactivity was observed in the milk of lactating rats following a 0.1 mg/kg subcutaneous dose of ^{3}H-AL-6221. Maximal levels were observed at 6 hours which then declined to < 3% of those at C_{max} by 24 hours which at this time were similar to those in maternal plasma (milk:plasma ratio 0.78).

MICROBIOLOGY

Not applicable.

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/day (or in mice given up to 100 mg/kg/day (several magnitudes higher than the maximum recommended human ocular dose (MRHOD) of 0.03 mcg/kg/day. No systemic effects were observed.

Ophthalmic solutions containing 0.004% travoprost (BAK-free) administered (one or two drops) to one eye, every half hour for ten doses on a single day resulted in no or only minimal to moderate ocular discomfort and demonstrated low irritation potential.

Repeated-Dose Sub-chronic, Chronic Toxicity

Repeated-dose systemic studies with travoprost were conducted in rats and mice with travoprost administered by the oral, intravenous, intraperitoneal, or subcutaneous routes. Study duration ranged from two weeks (mouse, oral) to six months (rat, subcutaneous). In the mouse, intravenous/intraperitoneal administration for up to 13 weeks had a NOAEL of 1000 mcg/kg. In the rat, subcutaneous administration of 30 and 100 mcg/kg for 6 months showed hyperostosis and fibrosis of bones examined (femur and sternum). Extramedullary hematopoiesis was

observed in the liver and spleen. Decreases in red blood cell parameters were also observed. The bone, spleen, liver and hematological changes were not observed in cynomolgus monkeys receiving travoprost by topical ocular administration for one year.

Repeat-dose topical ocular studies with travoprost (BAK-preserved) in rabbits (up to 6 months) and cynomolgus monkeys (1 year), showed no signs of ocular irritation or systemic toxicity at doses of up to 0.01 or 0.012%, respectively, when travoprost was administered up to three times a day to one eye. There was an increase in iris pigmentation and appearance of irregular corneal surface in the 1-year monkey study (all groups). In addition, a widened palpebral fissure was observed in those monkeys receiving travoprost. This observation has been noted in primates administered travoprost or other prostanoids such as latanoprost or bimatoprost.

Topical ocular toxicity of travoprost ophthalmic solutions (polyquaternium-1 preserved) was determined in a 3-month repeated-dose study in rabbits.

Table 14: Topical Ocular Repeated-Dose Studies Conducted with Travoprost Ophthalmic Solutions (polyquaternium-1 preserved)

Animal (Species) / Duration	Route	No. of Animals	Frequency	Dose	Result
Rabbit (NZW) / 3 months	Topical Ocular / OU	5 / sex / group	TID TID BID BID	Vehicle 20 mcg/mL 40 mcg/mL <u>120</u> mcg/mL	No significant toxicity

NZW = New Zealand White, TID = three times daily, BID = twice daily, OU = both eyes
No observed adverse effect level (NOAEL) is <u>underlined</u>.

There were no signs of ocular irritation and no significant effects on the intraocular pressure, corneal thickness or specular microscopy, no signs of systemic toxicity and no adverse clinical observations were observed. There were no significant alterations in clinical chemistry or histopathology. A NOAEL for travoprost ophthalmic solution polyquaternium-1preserved) was determined to be 120 mcg/mL when administered twice daily per eye for 3 months.

Carcinogenesis
Two year bioassays, in which rats and mice were dosed with travoprost by subcutaneous injection at doses up to 100 micrograms/kg/day (> 3000 times the MRHOD), revealed no evidence of carcinogenic effect.

Mutagenesis
Travoprost was not mutagenic in bacteria, in one mouse lymphoma assay, in the mouse micronucleus tests or 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 and 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 (> 300 times the MRHOD). 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 (100 times the MRHOD).

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 (> 30 and > 300 times the MRHOD respectively) with the lowest no effect level at 0.3 mcg/kg/day (10 times the MRHOD). The incidence of skeletal malformations was slightly increased in fetuses of rat dams receiving travoprost by subcutaneous injection at 10 mcg/kg/day (> 300 times the MRHOD), but not at 3 mcg/kg/day (100 times the MRHOD). No fetal abnormalities were observed in mice at 1.0 mcg/kg/day (> 30 times the MRHOD).

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 monitor activity parameters. The no-observed adverse effect level was 0.1 mcg/kg/day (> 3 times the MRHOD).

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READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

PrAPO-TRAVOPROST

Travoprost Ophthalmic Solution USP

Read this carefully before you start taking APO-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 APO-TRAVOPROST.

What is APO-TRAVOPROST used for?
APO-TRAVOPROST is used to treat high pressure in the eye. This pressure can lead to an illness called glaucoma.

High pressure in the eye(s). 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.

How does APO-TRAVOPROST work?
APO-TRAVOPROST is one of a group of medicines for glaucoma called prostaglandins. 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 APO-TRAVOPROST?
Medicinal ingredients: travoprost
Non-medicinal ingredients: polyquaternium-1 (preservative), boric acid, mannitol, polyoxyl 40 hydrogenated castor oil, propylene glycol, sodium chloride, sodium hydroxide and/or hydrochloric acid (to adjust pH) and water for injection.

APO-TRAVOPROST comes in the following dosage forms:
APO-TRAVOPROST is supplied as a 5 mL solution in a plastic bottle.

Do not use APO-TRAVOPROST if:
- You are allergic to travoprost or to prostaglandin analogues.
- You are allergic to any components of the APO-TRAVOPROST or its packaging (see **What are the ingredients in APO-TRAVOPROST?**).
- You are pregnant or planning on becoming pregnant.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take APO-TRAVOPROST. Talk about any health conditions or problems you may have, including if:
- You are breast-feeding or planning to breastfeed. APO-TRAVOPROST may get into your breast milk.
- You wear soft contact lenses.
- You are under 18 years of age.
- You had eye surgery or will be having eye surgery.
- You have an eye infection, eye irritation or suffer any damage to your eye(s).

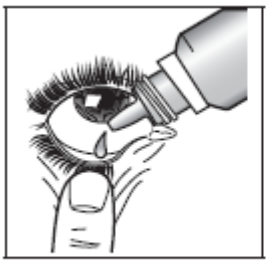
Other warnings you should know about:

- If you wear soft contact lenses, do not use APO-TRAVOPROST while wearing them. Wait 15 minutes after using APO-TRAVOPROST before you put your contact lenses back in.
- If APO-TRAVOPROST comes into contact with your skin, then it should be washed off right away.
- You may find that your vision is blurred for a short time after using APO-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.

The following may interact with APO-TRAVOPROST:
Drug interaction studies have not been done for APO-TRAVOPROST. There are no known interactions with APO-TRAVOPROST and other drugs. If you are currently, or have recently taken other medications, consult your health care provider.

How to take APO-TRAVOPROST:



1

2

- Get the APO-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 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 APO-TRAVOPROST at a time (picture 2).
- Put the bottle cap back on tightly after use.

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

If you are using other eye drops, wait at least 5 minutes between putting APO-TRAVOPROST, and the other eye drops, in your eye(s).

Usual dose:
Adults: 1 drop in your eye or eyes, once a day. Evening is the best time to take APO-TRAVOPROST.

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

Only use APO-TRAVOPROST in your eye(s).

Overdose:

If you think you have taken too much APO-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 APO-TRAVOPROST, take your next scheduled dose. Do not use a double dose to make up.

What are possible side effects from using APO-TRAVOPROST?
These are not all the possible side effects you may feel when taking APO-TRAVOPROST. If you experience any side effects not listed here, contact your healthcare professional.

Common side effects include eye redness, itching, irritation and dry eye.

- APO-TRAVOPROST may increase the length, thickness, colour and /or number of your eye lashes.
- APO-TRAVOPROST may change the colour of your eye. It may make your iris (the coloured part of your eye) more brown. This may occur slowly over a period of months.
- Increase in eyelash growth and change in eye colour may be permanent.

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	Hypersensitivity or allergic reaction including the signs or symptoms of rash, hives, swelling, or generalized itching			X
RARE	Unusual eye symptoms[a]		X	
	Asthma or trouble breathing		X	
	Changes in heart rate or rhythm		X	
	Chest pain		X	
	High or low blood pressure		X	

[a] Swelling of the back of your eye has been reported during treatment with Travoprost. The risk is higher in patients without their natural lens or who have had cataract surgery with a replacement lens

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

Store at 2°C - 25°C. Refrigeration is not required.

Protect from light. Keep bottle in outer cardboard packaging when not in use.

Do not use APO-TRAVOPROST for more than 125 days after opening the 5 mL bottle.

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

Keep out of reach and sight of children.

If you want more information about APO-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 (www.apotex.ca/products), or by contacting the sponsor, DISpedia, Apotex's Drug Information Service at 1-800-667-4708

This leaflet was prepared by Apotex Inc., Toronto, Ontario, M9L 1T9

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