PRODUCT MONOGRAPH

Pr LUMIGAN® PF

Bimatoprost Ophthalmic Solution, 0.03% w/v
(preservative free, supplied in single-dose containers)

Elevated Intraocular Pressure Therapy

Prostamide Analogue

Allergan Inc
Markham, ON
L6G 0B5

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Table of Contents

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Ophthalmic	preservative free solution, 0.03% w/v, supplied in single-dose containers	Not applicable *For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

LUMIGAN® PF (bimatoprost ophthalmic solution 0.03% w/v, preservative-free, supplied in single-dose conainers) 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 clinical differences in safety or effectiveness have been observed between elderly and other adult patients. Use as for adult patients.

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

CONTRAINDICATIONS

- 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.

DOSAGE AND ADMINISTRATION

Recommended Dose and Dosage Adjustment

The recommended dosage is one drop in the affected eye(s) once daily in the evening. The dosage of **LUMIGAN® PF** should not exceed once daily since it has been shown that more frequent administration of bimatoprost ophthalmic solution may lessen the intraocular pressure (IOP) lowering effect, and increase the frequency and severity of adverse events. (see WARNINGS and PRECAUTIONS, Ophthalmologic).

Missed Dose

Patients should be instructed to apply a single drop as soon as they remember, and then to return to their regular routine.

Administration

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

Contact lenses should be removed prior to instillation of **LUMIGAN® PF** and may be reinserted 15 minutes following its administration. (see WARNINGS and PRECAUTIONS, Ophthalmologic).

OVERDOSAGE

No information is available on overdosage in humans. If overdose with **LUMIGAN® PF** occurs, treatment should be symptomatic.

In short-term oral (by gavage) mouse and rat studies, doses up to 100 mg/kg/day did not produce any toxicity. This dose, expressed as mg/m^2, is at least 32 times higher than the amount of bimatoprost to which a 10 kg child would be exposed were it to accidentally ingest the entire content of a package (30 unit dose vials; 0.4 mL per vials; 12 mL) of **LUMIGAN® PF**.

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

WARNINGS AND PRECAUTIONS

General

Bimatoprost ophthalmic solutions have been reported to cause changes to pigmented tissue. The changes include increased pigmentation and growth of eyelashes and increased pigmentation of the iris and periorbital tissue (eyelid). The increased pigmentation may be permanent.

Bimatoprost ophthalmic solution may gradually change eye color, increasing the amount of brown pigment in the iris by increasing the number of melanosomes (pigment granules) in melanocytes. **The long-term effects on the melanocytes and the consequences of potential injury to the melanocytes and/or deposition of pigment granules to other area of the eye are currently unknown.** The change in iris color occurs slowly and may not be noticeable for several months to years. Pigmentation is expected to increase as long as bimatoprost ophthalmic solution is administered. Noticeable darkening of the iris has been reported in 1.5% of patients treated for 12 months with bimatoprost ophthalmic solution 0.03% (with benzalkonium chloride 0.05 mg/mL as preservative) at the proposed dose of one drop once daily in each affected eye (1.1% of patients treated for 6 months).

Patients should be informed of the possibility of iris color change. In addition, patients who are expected to receive treatment in only one eye should be informed about the potential for increased brown pigmentation of the iris, periorbital tissue, and eyelashes in the treated eye and thus, heterochromia between the eyes. They should be advised of the potential for a disparity between the eyes in length, thickness, and/or number of eyelashes.

Typically the brown pigmentation around the pupil is expected to spread concentrically towards the periphery in affected eyes, but the entire iris or parts of it may also become more brownish. Until more information about increased brown pigmentation is available, patients should be examined regularly and, depending on the clinical situation, treatment may be stopped if increased pigmentation ensues. The increase in brown iris pigment is not expected to progress further upon discontinuation of treatment, but the resultant color change is likely to be permanent. Neither nevi nor freckles of the iris are expected to be affected by treatment.

There is the potential for hair growth to occur in areas where bimatoprost solution comes repeatedly in contact with the skin surface. Thus, it is important to apply bimatoprost as instructed and to avoid it running onto the cheek or other skin areas.

Each vial is intended only for a single treatment in the affected eye(s). Discard any remaining solution in the vial immediately after use.

Carcinogenesis and Mutagenesis

See TOXICOLOGY.

Hepatic/Biliary/Pancreatic

LUMIGAN® PF has not been studied in patients with moderate to severe hepatic impairment and should therefore be used with caution in such patients. In patients with a history of mild liver disease or abnormal alanine aminotransferase (ALT), aspartate aminotransferase (AST) and/or bilirubin at baseline, bimatoprost 0.03% (with benzalkonium chloride 0.05 mg/mL as preservative) had no adverse effect on liver function over 48 months.

Occupational Hazards

Based on the pharmacodynamic profile, bimatoprost is not expected to influence a patient's ability to drive or operate machinery. As with any ocular medication, if transient blurred vision occurs at instillation, the patient should wait until the vision clears before driving or using machinery.

Ophthalmologic

LUMIGAN® PF should be used with caution in patients with active intraocular inflammation (e.g. uveitis) because the inflammation may be exacerbated.

Macular edema, including cystoid macular edema, has been reported during treatment with bimatoprost ophthalmic solution 0.03% (with benzalkonium chloride 0.05 mg/mL as preservative). **LUMIGAN® PF** should be used with caution in aphakic patients, in pseudophakic patients with a torn posterior lens capsule, or in patients with known risk factors for macular edema (e.g. intraocular surgery, retinal vein occlusions, ocular inflammatory disease and diabetic retinopathy).

LUMIGAN® has not been studied in patients with inflammatory ocular conditions, neovascular, inflammatory, angle-closure glaucoma, congenital glaucoma or narrow-angle glaucoma.

Limited experience is available with the use in patients with open-angle glaucoma with pseudoexfoliative and pigmentary glaucoma, and chronic angle-closure glaucoma with patent iridotomy.

In **LUMIGAN®** 0.03% studies in patients with glaucoma or ocular hypertension, it has been shown that more frequent exposure of the eye to more than one dose of bimatoprost daily may decrease the IOP lowering effect. There is a potential for the IOP-lowering effect of prostaglandin analogs (e.g., **LUMIGAN®**) to be reduced in patients with glaucoma or ocular hypertension when used with other prostaglandin analogs. Patients using **LUMIGAN®** with other prostaglandin analogs should be monitored for changes to their IOP.

LUMIGAN® PF has not been studied in patients wearing contact lenses. Contact lenses should be removed prior to instillation of **LUMIGAN® PF** and may be reinserted 15 minutes following its administration.

Cases of corneal calcification have been reported very rarely in association with the use of phosphate containing eye drops in some patients with significantly damaged corneas.

Renal

LUMIGAN® PF has not been studied in patients with renal impairment and should therefore be used with caution in such patients.

Sexual Function/Reproduction

Bimatoprost did not impair fertility in male or female rats at doses of up to 0.6 mg/kg/day (approximately 103 times the human exposure based on blood area under the curve (AUC) levels obtained in subjects administered bimatoprost ophthalmic solution 0.03% (with benzalkonium chloride 0.05 mg/mL as preservative), one drop/day in both eyes for 14 days).

Special Populations

Pregnant Women: In embryo/fetal developmental studies in pregnant mice and rats, abortion was observed at oral doses of bimatoprost which were at least 33 or 97 times, respectively, the intended human exposure as measured by blood AUC levels obtained in subjects administered bimatoprost ophthalmic solution 0.03% (with benzalkonium chloride 0.05 mg/mL as preservative), one drop/day in both eyes for 14 days.

Maternal toxicity, evidenced by reduced gestation length, late resorptions, fetal death, postnatal mortality and reduced pup body weights were observed when female rats received oral doses which were at least 41 times the intended human exposure (based on blood AUC levels obtained in subjects administered bimatoprost ophthalmic solution 0.03% (with benzalkonium chloride 0.05 mg/mL as preservative), one drop/day in both eyes for 14 days). Cohabitation times in the offspring were increased but neurobehavioural functions were not affected.

There are no adequate and well-controlled studies of **LUMIGAN® PF** administration in pregnant women. Because animal reproductive studies are not always predictive of human response, **LUMIGAN® PF** should be administered during pregnancy only if the potential benefit justifies the potential risk to the fetus.

There has been no experience of pregnancy during clinical trials.

Nursing Women: It is not known whether bimatoprost is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when **LUMIGAN® PF** is administered to a nursing woman.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

A multicenter, double-masked, parallel-group, active-controlled study designed to compare the efficacy and safety of **LUMIGAN® PF** (without benzalkonium chloride) with **LUMIGAN®** 0.03% (with benzalkonium chloride) once-daily for 12 weeks demonstrated that the 2 formulations had similar safety profiles. The most frequently reported adverse event was conjunctival hyperaemia (23.9% of patients treated).

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*.

The data presented below are taken from a randomized, multicenter, double-masked, parallel-group clinical study, of 12 weeks duration, which was conducted in 597 patients with glaucoma or ocular hypertension. A summary of the most common ocular adverse events observed in this study (incidence ≥ 1.0%), regardless of causality, is presented in the Table 1.

Table 1 Number (%) of Patients with Ocular Adverse Events, Regardless of Causality, Reported by ≥ 1% of Patients in Any Treatment Group

System Organ Class Preferred Term	LUMIGAN® PF N= 301	LUMIGAN® 0.03% N= 295
Eye disorders		
Conjunctival hyperemia	72 (23.9%)	77 (26.1%)
Eye pruritus	12 (4.0%)	12 (4.1%)
Punctate keratitis	9 (3.0%)	9 (3.1%)
Foreign body sensation in eyes	7 (2.3%)	2 (0.7%)
Dry eye	5 (1.7%)	9 (3.1%)
Growth of eyelashes	5 (1.7%)	1 (0.3%)
Eye pain	4 (1.3%)	3 (1.0%)
Eye irritation	3 (1.0%)	4 (1.4%)
Erythema of eyelid	3 (1.0%)	1 (0.3%)
Skin and subcutaneous tissue disorders		
Skin hyperpigmentation	3 (1.0%)	2 (0.7%)

Source: CSR 192024-048, Table 14.3-3

In this study, one or more adverse events, regardless of causality, were reported by a numerically lower proportion of patients in the **LUMIGAN® PF** group (40.5%) compared with **LUMIGAN®** (44.1%). The most frequent treatment-related adverse events were conjunctival hyperaemia, eye pruritus, and punctate keratitis. The majority of cases of hyperaemia were graded as trace to mild on macroscopic evaluation. No safety concerns were noted from other ocular assessments.

Overall, 5 patients discontinued due to adverse events: 0.7% (2/301) of patients in the **LUMIGAN® PF** group and 1.0% (3/295) in the **LUMIGAN®** group.

Less Common Clinical Trial Adverse Drug Reactions (<1%)

The following adverse events were observed with an incidence rate < 1% for **LUMIGAN® PF**:

Eye Disorders: Vision blurred, hair growth abnormal, iris hyperpigmentation, lacrimation increased, conjunctival edema, asthenopia, eyelids pruritus, eyelid edema, photophobia
Nervous System Disorders: Headache

Post-Market Adverse Drug Reactions
The following adverse reactions have been identified during postmarketing use of **LUMIGAN® PF**. Because postmarketing reporting is voluntary and from a population of uncertain size, it is not possible to reliably estimate the frequency of these reactions.

Eye disorders: Eye discharge, ocular discomfort
Immune system disorders: Hypersensitivity reaction including signs and symptoms of eye allergy and allergic dermatitis
Nervous system disorders: Dizziness
Respiratory, thoracic and mediastinal disorders: Asthma, Exacerbation of Asthma, Dyspnea
Vascular disorders: Hypertension

DRUG INTERACTIONS

Overview
No specific drug interaction studies have been conducted.

Drug-Drug Interactions
No drug-drug interactions are anticipated in humans since systemic drug concentrations of bimatoprost are extremely low (less than 0.2 ng/mL) following repeated ocular dosing with bimatoprost ophthalmic solution 0.03% (with benzalkonium chloride 0.05 mg/mL as preservative) and as metabolism and excretion involves multiple pathways.

In clinical studies, **LUMIGAN®** 0.03% (with benzalkonium chloride) was used concomitantly with a number of different ophthalmic beta-blocking agents without evidence of interactions. Concomitant use of **LUMIGAN®** and antiglaucomatous agents other than topical beta-blockers has not been evaluated during adjunctive glaucoma therapy.

There is a potential for the IOP lowering effect of prostaglandin analogs (e.g., **LUMIGAN®**) to be reduced in patients with glaucoma or ocular hypertension when used with other prostaglandin analogs (see WARNINGS AND PRECAUTIONS, Ophthalmologic).

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.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action
Bimatoprost is a synthetic prostamide analogue and is structurally related to prostaglandin F2α in that the carboxylic acid group is replaced with an electronically neutral substituent. Its mechanism of action resembles that of prostamide F2α, a naturally occurring substance. Bimatoprost exhibits no meaningful pharmacological activity at known prostaglandin receptors as well as no uterotonic or mitogenic activity. Studies suggest that it lowers IOP by increasing uveoscleral and trabecular meshwork outflow, with no significant effect on aqueous humor inflow. Pharmacodynamic studies in humans demonstrated a significant 30-35% decrease in outflow resistance compared to vehicle treated eyes based on tonographic data and calculated values of apparent outflow resistance. The ocular hypotensive effect does not involve a COX-dependent mechanism.

Pharmacodynamics
The effect of bimatoprost ophthalmic solution 0.03% (with benzalkonium chloride 0.05 mg/mL as preservative) within the first 12 hours of dosing was evaluated in two studies. When dosed in the morning, bimatoprost began to take effect within 4 hours after initial instillation, and was followed by continued decreases in IOP through 12 hours. The effect of bimatoprost 0.03% ophthalmic solution (with benzalkonium chloride 0.05 mg/mL as preservative) between 12 and 24 hours post-instillation also was evaluated. Mean IOP at 12 hours post-dosing was 17.7 mm Hg and 16.9 mm Hg 24 hours after the last dose. Based on this information, once-daily evening dosing is recommended so that the time of anticipated maximal efficacy of the drug coincides with the morning hours (08:00 to 11:00 AM) when untreated IOP is usually highest.

Pharmacokinetics

After one drop of bimatoprost ophthalmic solution 0.03% (with benzalkonium chloride 0.05 mg/mL as preservative) was administered once daily to both eyes of 15 healthy subjects, blood bimatoprost concentrations peaked within 10 minutes after dosing and were below the lower limit of detection (0.025 ng/mL) in most subjects within 1.5 hours after dosing.

Systemic exposure after repeated ocular application is low. Steady state was achieved after one week of once daily dosing with one drop of bimatoprost ophthalmic solution 0.03% (with benzalkonium chloride 0.05 mg/mL as preservative) to both eyes, with mean Cmax values of 0.07 and 0.08ng/mL on day 7 and 14, respectively, and mean AUC 0-24h of 0.074 and 0.096 ng•hr/mL on day 7 and 14, respectively.

In patients with glaucoma or ocular hypertension, bimatoprost blood concentrations were similar to those observed in normal healthy subjects.

There was no significant systemic drug accumulation over time with the once daily dosing regimen. Mean blood concentration was around 0.08 ng/mL after 12 months of QD or BID dosing with bimatoprost ophthalmic solution 0.03% (with benzalkonium chloride 0.05 mg/mL as preservative). The once daily regimen corresponded to a total exposure of 6.13 mg (one 28 µL drop in each eye once a day for 12 months) or 0.00028 mg/kg/day for a 60-kg individual over 12 months.

Absorption: Bimatoprost is rapidly absorbed across the human cornea and sclera, with scleral penetration being more efficient. Animal studies show that it is well distributed into ocular tissues following ocular administration, where only minimal metabolism occurs in humans.

Distribution: Bimatoprost is moderately distributed into body tissues with a steady-state volume of distribution of 0.67 L/kg. In human blood, bimatoprost resides mainly in the plasma. Approximately 12% of bimatoprost remains unbound in human plasma.

Metabolism: Bimatoprost is the major circulating species in the blood once it reaches the systemic circulation following ocular dosing. Bimatoprost then undergoes oxidation, N-deethylation and glucuronidation to form a diverse variety of metabolites. Studies using human liver microsomes and recombinant human P450 isozymes, identified CYP 3A4 as one of the enzymes involved in the metabolism of bimatoprost in humans. However, since multiple enzymes and pathways are involved in the biotransformation of bimatoprost, no significant drug-drug interactions are anticipated.

Bimatoprost is only minimally metabolized in ocular tissues in humans, and is active in its intact form, without metabolic modification.

Excretion: Following an intravenous dose of radiolabelled bimatoprost (3.12 µg/kg) to six healthy subjects, the maximum blood concentration of unchanged drug was 12.2 ng/mL and decreased rapidly with an elimination half-life of approximately 45 minutes. The total blood clearance of bimatoprost was 1.5 L/hr/kg. Up to 67% of the administered dose was excreted in the urine while 25% of the dose was recovered in the feces. Both urinary and fecal routes are important pathways for elimination of the parent compound and its metabolites, following intravenous administration.

Special Populations and Conditions

Geriatrics: Elderly individuals (>65 years) exhibited higher systemic levels but this was not considered to be clinically relevant since no overall clinical differences in safety or effectiveness have been observed between elderly and other adult patients.

STORAGE AND STABILITY

LUMIGAN® PF should be stored in the original container at 15º-25ºC. Keep in a safe place out of the reach of children. Do not freeze.

Once the tray is opened, the single-dose containers (vials) should be used within 30 days.

DOSAGE FORMS, COMPOSITION AND PACKAGING

LUMIGAN® PF is a sterile ophthalmic solution.

Each mL of **LUMIGAN® PF** contains bimatoprost 0.3 mg with the following non-medicinal ingredients: sodium chloride, sodium phosphate dibasic heptahydrate, citric acid monohydrate, and purified water. Sodium hydroxide and/or hydrochloric acid may be added to adjust pH.

LUMIGAN® PF is supplied sterile in a 0.9 mL vial manufactured from low-density polyethylene (LDPE). Each vial is filled to a volume of 0.4 mL. Each commercial pack contains 30 vials and each physician sample pack contains 5 vials.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

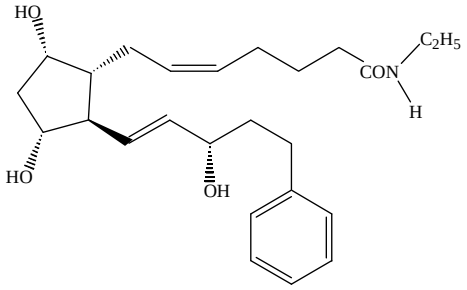
Drug Substance

Proper name: bimatoprost

Chemical name: (Z)-7-[(1R,2R,3R,5S)-3,5-Dihydroxy-2-[1E,3S)-3-hydroxy-5-phenyl-1-pentenyl]cyclopentyl]-5-N-ethylheptenamide

Molecular formula and molecular mass: $C_{25}H_{37}NO_4$; 415.58

Structural formula:



Physicochemical properties: Bimatoprost is a white to off-white powder, which is very soluble in ethyl alcohol and methyl alcohol and slightly soluble in water.

CLINICAL TRIALS

Study demographics and trial design

A double-masked, randomized, parallel group study compared the efficacy and safety of once-daily (evening) administration of **LUMIGAN® PF** (without benzalkonium chloride) with **LUMIGAN®** (with benzalkonium chloride) for 12 weeks in patients with glaucoma or ocular hypertension. Of the 596 patients treated, 301 received **LUMIGAN® PF** and 295 patients received **LUMIGAN®**.

Table 2 - Summary of patient demographics for study 192024-048

Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range)	Gender
Phase 3 double-masked, randomized, active-controlled, parallel group	**LUMIGAN® PF** **LUMIGAN®** Ophthalmic; One drop every evening for 12 weeks	**LUMIGAN® PF** : (n = 302) **LUMIGAN®**: (n = 295)	64.8 years (29 to 92 years)	M: 246 F: 351

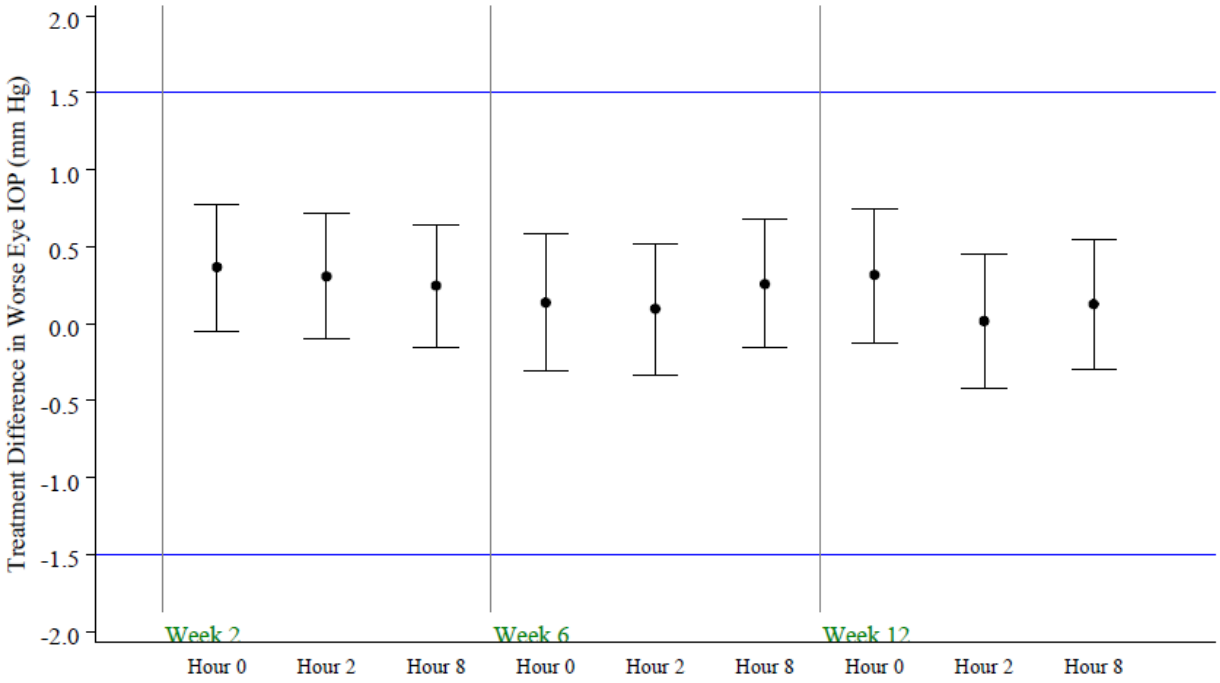
Of the 597 enrolled patients (ITT population), 98.0% (585/597) completed the study. The mean age of patients was 64.8 years (range 29 to 92 years). The majority of patients were female (58.8%, 351/597) and Caucasian (71.2%, 425/597).

The primary population for the efficacy analyses was the PP population. The primary efficacy variable was derived from the IOP measurements. The primary efficacy analysis was the change from baseline (follow-up minus baseline) in worse eye IOP at each hour evaluated (hours 0, 2, and 8) at week 12 using the PP population. The treatments were compared using the ANCOVA model with treatment and investigator as the main effects and baseline worse-eye IOP as the covariate. A 2-sided 95% confidence interval (CI) for the treatment difference (**LUMIGAN® PF** minus **LUMIGAN®**) was constructed from the ANCOVA model for each timepoint analyzed. The hypothesis was that **LUMIGAN® PF** is noninferior to **LUMIGAN®** at the week 12 visit. Non-inferiority would be declared if **LUMIGAN® PF** was noninferior to **LUMIGAN®** at each hour evaluated (hours 0, 2, and 8) at week 12. **LUMIGAN® PF** was considered to be noninferior to **LUMIGAN®** at the timepoint if the upper limit of the 95% CI did not exceed 1.5 mm Hg.

Study results

For the primary analysis, **LUMIGAN® PF** was considered to be non-inferior to **LUMIGAN®** at each hour evaluated (hours 0, 2 and 8) during the week 12 visit for worse eye IOP change from baseline: upper limit of the 95% CI for between-treatment difference (**LUMIGAN® PF** minus **LUMIGAN®**) did not exceed 1.5 mm Hg (as well as not exceeding 1.0 mm Hg) in the PP population (Figure 1). In fact, the upper limit did not exceed 0.75 mm Hg at any week 12 timepoint. Non-inferiority was also demonstrated for the ITT population. Both treatments studied showed statistically and clinically significant mean decreases from baseline in worse eye IOP at all follow-up timepoints ($p < 0.001$).

Figure 1 **Mean and 95% Confidence Interval for Treatment Difference (LUMIGAN® PF minus LUMIGAN®) Change from Baseline in Worse Eye IOP (mm Hg) at Each Postbaseline Timepoint (PP Population)**



Note: Bars at each hour denote the 95% CIs, which are based on the ANCOVA model with treatment and investigator as fixed effects and baseline worse eye IOP as the covariate. Estimated difference (**LUMIGAN® PF** minus **LUMIGAN®**) was based on the least-squares means from the ANCOVA model.

Source: CSR 192024-048, Figure 14.2-4.

The mean changes from baseline in worse eye IOP for the PP population are summarized in Table 3.

Table 3 Mean Change from Baseline in Worse Eye IOP (mm Hg) (PP Population)

Visit	Timepoint	Statistics	LUMIGAN® PF (N=295)	LUMIGAN® (N=291)	LUMIGAN® PF – LUMIGAN® Difference, 95% CI [a]
Week 2	Hour 0	N	283	281	0.37
		Mean	–7.22	–7.55	(–0.05, 0.78)
		SD	2.845	2.968	
	Hour 2	N	282	279	0.31
		Mean	–6.85	–7.17	(–0.10, 0.72)
		SD	3.217	2.922	
	Hour 8	N	283	280	0.25
		Mean	–6.03	–6.27	(–0.15, 0.64)
		SD	3.160	3.399	
Week 6	Hour 0	N	276	277	0.14
		Mean	–7.43	–7.58	(–0.30, 0.58)
		SD	2.783	3.089	
	Hour 2	N	275	276	0.10
		Mean	–7.01	–7.14	(–0.33, 0.52)
		SD	3.059	3.122	
	Hour 8	N	276	277	0.26
		Mean	–6.02	–6.34	(–0.15, 0.68)
		SD	3.291	3.407	
Week 12	Hour 0	N	281	274	0.32
		Mean	–7.49	–7.77	(–0.12, 0.75)
		SD	2.900	3.029	
	Hour 2	N	279	272	0.02
		Mean	–7.06	–7.11	(–0.42, 0.45)
		SD	3.333	3.192	
	Hour 8	N	279	272	0.13
		Mean	–5.93	–6.06	(–0.29, 0.55)
		SD	3.432	3.602	

CI = confidence interval; SD = standard deviation.

[a] CIs are based on the ANCOVA model with treatment and investigator as main effects and baseline worse eye IOP as the covariate. Estimated difference (**LUMIGAN® PF** minus **LUMIGAN®**) was based on the least-squares means from the ANCOVA model.

Source: CSR 192024-048, Table 14.2-4.2

Both treatments studied showed statistically and clinically significant mean decreases from baseline in worse eye IOP at all follow-up timepoints ($p < 0.001$). Mean changes from baseline IOP ranged from –7.49 to –5.93 mm Hg for **LUMIGAN® PF**, and from –7.77 to –6.06 mm Hg for **LUMIGAN®** across the study as measured on weeks 2, 6, and 12 (hours 0, 2, and 8) in the PP population (Table 3).

DETAILED PHARMACOLOGY

Animal Pharmacology

Ocular Studies

Studies in ocular normotensive and laser-induced ocular hypertensive cynomolgus monkeys indicated that bimatoprost potently reduces intraocular pressure. Five-day studies in ocular normotensive monkeys and one day studies in ocular hypotensive monkeys demonstrated that a 0.001% w/v dose of bimatoprost could significantly lower intraocular pressure. Five day studies in ocular normotensive Beagle dogs confirmed bimatoprost as a potent ocular hypotensive over a dose range of 0.001% to 0.1% w/v when given either once daily or twice daily.

Bimatoprost did not alter pupil diameter in monkeys at the 0.1% dose. This is in contrast to Beagle dog studies, where 0.001% to 0.1% w/v doses produced miosis.

Morphologic changes in the anterior eye segment of cynomolgus monkeys unilaterally topically treated for one year with either latanoprost 0.005%, bimatoprost 0.03%, or two prostaglandin EP agonists were investigated. The general morphology of the ciliary muscle and trabecular meshwork was normal in appearance and shape in all animals, whereas similar localized morphologic changes were observed in all four treatment groups. The enlargement of uveoscleral outflow routes and morphologic changes in the trabecular meshwork may be suggestive of increased uveoscleral and conventional outflow. In the affected ciliary muscle areas, sprouting of nerve fibers may be the consequence of tissue remodeling.

Cardiovascular Effects

Bimatoprost given by single intravenous injection at up to 10 µg/kg to dogs, by intravenous injection at up to 1 mg/kg/day for 17 weeks to monkeys, or by topical ocular instillation at up to 0.1%/drop/day for 52 weeks to monkeys did not cause cardiovascular effects. In particular, there was no change in the QTc interval.

Metabolism and Pharmacokinetics

Ocular Pharmacokinetics

Following a single ocular instillation of ^{3}H-bimatoprost to rabbits and single and multiple ocular instillations to monkeys, bimatoprost was absorbed rapidly and was well distributed in the eye. The absorbed radioactivity was found mainly in the anterior segment of the eye and the highest concentrations of radioactivity were found in the conjunctiva, cornea, sclera, iris, and ciliary body in both rabbit and monkey eyes. Maximal concentrations in these tissues were reached

within 0.5 to 2 hours post-dose. Twenty-four hours after the last dose in monkeys, bimatoprost concentrations in the ciliary body (the purported site of action) were still over 5-fold higher than the *in vitro* EC_{50} value of 14 ng/mL required for pharmacological effect.

Systemic Absorption Following Ocular and Oral Administration

Bimatoprost was systemically absorbed after ophthalmic administration to rabbits and monkeys. The C_{max} in plasma was 3.23 ng-eq/mL in monkeys following twice-daily ocular administration of 0.1% bimatoprost for 10 days and 6.28 ng-eq/mL in rabbits following a single administration of 0.1%. The oral bioavailability of bimatoprost was 40%, 29% and 3% in mice, rats and monkeys, respectively. The low oral bioavailability in monkeys was attributed to extensive first-pass metabolism.

Systemic Disposition after Intravenous Administration

Following intravenous administration to mice, rats and monkeys bimatoprost had a moderate apparent volume of distribution at steady state ranging from 2.1 to 6.0 L/kg. Bimatoprost had a mean residence time of 0.28 hr in mice, 0.42 hr in rats and 0.93 hr in monkeys, indicating that bimatoprost was rapidly eliminated in all three species. The mean blood clearance was 12, 9.5 and 2.4 L/hr/kg, respectively. In mice and rats, total blood clearance appeared to be greater than liver blood flow, indicating the involvement of extrahepatic metabolism.

Systemic Tissue Distribution

The unbound fraction of bimatoprost in mouse, rat, rabbit and monkey plasma ranged from 28 to 37% *in vitro*. The *in vitro* binding of bimatoprost to synthetic melanin was not extensive at approximately 20%, and was reversible. Following intravenous administration of ^{3}H-bimatoprost to rats, either as a single dose or after daily injections for 21 days, radioactivity was rapidly distributed to all tissues and organs examined. The highest concentrations of radioactivity were seen in the gastrointestinal tract, liver, kidney and urinary bladder. The blood-to-plasma ratio of radioactivity was 0.75, indicating that bimatoprost remained in the plasma portion of the blood. By 168 hours post-dose, all radioactivity in the body was accounted for by tritiated water, and not by bimatoprost or its metabolites. Following a single intravenous administration of ^{3}H-bimatoprost to pregnant rats, there was a low, but quantifiable, amount of drug transfer into the placenta, amniotic fluid and fetus. Following intravenous administration of ^{3}H-bimatoprost to lactating rats, the concentrations of radioactivity found in milk were similar to those seen in plasma. Therefore the amount of drug related material transferred into milk at the clinical dose level is expected to be extremely low.

Ocular Metabolism

After ophthalmic administration, bimatoprost was extensively metabolized in all of the ocular tissues in the rabbit eye. In contrast, bimatoprost, at exaggerated doses, was only minimally metabolized in the monkey eye following ophthalmic administration.

Systemic Metabolism

Following a single intravenous administration to rats and monkeys, bimatoprost was extensively metabolized by glucuronidation, hydroxylation, deamidation and N-deethylation, with glucuronidated metabolites accounting for the majority of the drug-related material in the blood, urine and faeces of both species. In pregnant rats, at least 22 metabolites were detected in the maternal tissues following a single intravenous administration of ^{3}H-bimatoprost. The C1-acid metabolite of bimatoprost was the major species detected in the uterus and ovaries (about 45% of total radioactivity), while bimatoprost was the major species detected in the fetus (about 50% of total radioactivity). The C-1 acid is the major metabolite in rats and rabbits, but not in dogs, monkeys, or humans. Following one month of daily intravenous administration to rats and monkeys, bimatoprost was found to have no clinically significant effect on any of the hepatic drug metabolizing enzymes tested. In studies using recombinant human P450 enzymes, CYP3A4/5 were identified as the most important Cytochrome P450 enzymes involved in the hydroxylation of bimatoprost.

Excretion

Both the urinary and fecal routes are important pathways for excretion of bimatoprost and its metabolites in rats and monkeys. Following a single intravenous administration of ^{3}H-bimatoprost to rats, the urinary excretion of radioactivity was 42% of the dose in females and 27% in males, while the faecal excretion of radioactivity was 49% in females and 69% in males. Following a single intravenous administration of ^{3}H-bimatoprost in monkeys, male and females excreted 58 and 64% of the dose into the urine and 24 and 31% into the faeces, respectively. The mean total recovery of radioactivity was >90% for both genders.

<u>Human Pharmacology</u>

Pharmacodynamics

Dosage Determination Studies for Treatment of Elevated IOP

Four Phase 2 dose-ranging studies were conducted in patients with open-angle glaucoma or ocular hypertension. A dose-response study in 60 patients with twice-daily dosing for 5 ± 2 days showed significant reductions from baseline IOP with bimatoprost 0.01% w/v and 0.03% w/v formulations as well as with timolol 0.5% w/v, compared to vehicle. Among the

bimatoprost concentrations evaluated, 0.03% w/v had the best ratio of safety to efficacy, and the 24-hour post-dose results suggested the potential for efficacy with once-daily dosing.

The effects of 0.003%, 0.01% and 0.03% w/v bimatoprost (nonpreserved formulations) and of twice-daily versus once-daily (evening) dosing were compared to timolol 0.5% w/v and vehicle in 100 patients treated for one month. Although 0.01% w/v and 0.03% w/v had similar safety profiles, 0.03% w/v had significantly better efficacy. There was no significant difference in efficacy between twice-daily and once-daily dosing.

A study in 106 patients evaluated once-daily evening dosing for 28 days with bimatoprost 0.03% w/v (preserved and nonpreserved formulations), AGN 192151 0.06% w/v (a congener of bimatoprost), latanoprost 0.005% w/v, and vehicle. Although the sample size was small, bimatoprost and latanoprost appeared to exhibit comparable safety profiles. The profiles were similar with the preserved and nonpreserved formulations of bimatoprost 0.03% w/v. The mean reduction in IOP are shown in Table 4.

Table 4: Mean Reduction in Intraocular Pressure (mm Hg) from Baseline B Day 29

0.03% w/v Bimatoprost Non-preserved n=21	0.03% w/v Bimatoprost Preserved n=21	Latanoprost n=22	Vehicle Non-preserved n=21
8.9 ± 0.7	8.0 ± 0.9	7.6 ± 0.5	1.7 ± 1.2

A study in 32 patients evaluated once-daily morning dosing for 28 days with bimatoprost 0.03% w/v or vehicle. The ocular hypotensive effect of bimatoprost 0.03% w/v with once-daily morning dosing was similar to that observed with once-daily evening dosing.

In the Phase 2 dose-response studies, bimatoprost 0.03% w/v provided greater lowering of IOP than 0.003%, 0.01%, or 0.1% w/v, with similar number of treatment-related adverse events as the 0.01% w/v concentration. Thus the 0.03% w/v concentration was selected for evaluation in Phase 3 studies. Significant IOP-lowering effects were shown for this concentration with once-daily dosing.

The effect of bimatoprost 0.03% w/v within the first 12 hours of dosing was evaluated in two studies. When dosed in the morning, bimatoprost began to take effect within 4 hours after initial instillation, and was followed by continued decreases in IOP through 12 hours. The effect of bimatoprost 0.03% w/v between 12 and 24 hours post-instillation was evaluated. At baseline, the mean IOP of bimatoprost was approximately 26 mm Hg. At 12 hours post-dosing it was 17.7 mm Hg and at 24 hours post-dosing it was 16.9 mm Hg.

Based on this information, once-daily evening dosing was selected for the Phase 3 studies so that the time of anticipated maximal efficacy of the drug coincided with the morning hours (08:00 to 11:00 AM) when untreated IOP is usually highest.

Pharmacokinetics

Absorption and Systemic Drug Exposure

Bimatoprost penetrates the human cornea and sclera well *in vitro*. The mean corneal permeability coefficient was 3.24 x 10-6 cm/sec. Bimatoprost penetrated human scleral tissue better than corneal tissue with a mean scleral permeability coefficient of 14.5 x 10^{-6} cm/sec.

After one drop of 0.03% w/v ophthalmic solution was administered once daily to both eyes of 15 healthy subjects for two weeks, blood bimatoprost concentrations were below the lower limit of detection (0.025 ng/mL) in most subjects within 1 to 1.5 hours after dosing. Mean bimatoprost Cmax values were similar on days 7 and 14 at 0.0721, and 0.0822 ng/mL, respectively. The mean AUC_{0-24} hr values were also similar on days 7 and 14 at 0.0742, and 0.096 ng•hr/mL, respectively, indicating that a steady systemic exposure to bimatoprost had been reached during the first week of ocular dosing.

The blood concentrations of bimatoprost from patients with open angle glaucoma or ocular hypertension in two Phase 3 safety and efficacy studies were measured (N=88 on once-daily treatment and N=89 on twice-daily treatment). The samples were collected at approximately 5 minutes after the evening dose over a 3-month treatment period. Bimatoprost blood concentrations were similar to those observed in normal, healthy subjects and there was no significant systemic drug accumulation over time. The C-1 acid metabolite (AGN 191522) was typically not measurable in blood samples from these studies.

Therapeutic drug monitoring in the Phase 3 studies showed that in one study that the elderly group had a higher concentration in the blood; however, this was not observed in the second Phase 3 study.

There was no significant systemic accumulation of bimatoprost following twice-daily dosing for 7 days in either young (18-44 years, mean = 28.5) or elderly patients (65-80 years, mean = 71.0). Bimatoprost appeared rapidly in the blood in both age groups, and was below the LLOQ by 1.5 hours in most patients. Systemic exposure was higher in the elderly than the young following both single and multiple dosing (124% and 213%, respectively). The mean AUC_{0-24} hr value of 0.0634 ng•hr/mL in elderly subjects was statistically significantly higher than that of 0.0218 ng•hr/mL in young subjects, suggesting the existence of an age effect. However, this finding is not considered clinically relevant as bimatoprost exhibits similar efficacy and safety profiles in both the young and elderly populations.

Distribution

Bimatoprost is moderately distributed into body tissues with a steady-state volume of distribution of 0.67 L/kg. In human blood, bimatoprost resides mainly in the plasma. Approximately 12% of bimatoprost remain unbound in human plasma. The *in vitro* binding of

bimatoprost to synthetic melanin was ~20% at concentrations of 0.2 - 100 µg/mL. The overall extent of melanin binding was not dependent on concentration, and the binding was reversible.

Metabolism

Bimatoprost is the major circulating species in the blood once it reaches the systemic circulation following ocular dosing. Bimatoprost then undergoes oxidation, N-deethylation and glucuronidation to form a diverse variety of metabolites.

Elimination

Following an intravenous dose of radiolabelled bimatoprost (3.12 µg/kg) to six healthy subjects, the maximum blood concentration of unchanged bimatoprost was 12.2 ng/mL and declined rapidly with an elimination half-life of 0.771 hour (approximately 45 minutes). Blood concentrations of AGN 191522, the C-1 acid metabolite, were much lower than those of bimatoprost as peak concentration was 0.12 ng/mL. The total blood clearance (Clb) of unchanged bimatoprost was 1.50 L/hr/kg.

Sixty-seven percent of the administered dose of bimatoprost was excreted in the urine with only a small fraction excreted as unchanged drug. Twenty-five percent of the dose was recovered in feces of which 15-40% was eliminated as unchanged drug.

TOXICOLOGY

The acute toxicity of bimatoprost was evaluated in single intraperitoneal and intravenous (IV) dose studies in mice and rats. A dose of 96 mg/kg administered intraperitoneally to mice, and up to 3 mg/kg IV administered to rats produced no adverse effects.

Long-term Toxicity

No treatment-related ocular or systemic effects were produced in Dutch belted rabbits when 0.03% or 0.1% bimatoprost ophthalmic formulation was instilled to the eye once or twice daily for 6 months. The highest dose (0.1% twice daily) produced 53 times the systemic drug exposure seen in humans treated with 1 drop in each eye of bimatoprost ophthalmic solution 0.03% once daily for 2 weeks. No treatment-related systemic effects were observed in cynomolgus monkeys when 0.03% or 0.1% bimatoprost ophthalmic formulation was instilled to the eye once or twice daily for 1 year. An increase in iris pigmentation was noted in some animals in all treated groups. No associated increase in melanocyte number was observed with the pigmentation. It appears that the mechanism of increased iris pigmentation is due to increased stimulation of melanin production in melanocytes and not to an increase in melanocyte number. Reversible dose-related periocular effects characterized by a prominent upper and/or lower sulcus and widening of the palpebral fissure of the treated eye was also

observed. No functional or microscopic change related to the periocular change was observed. The highest dose (0.1% twice daily) produced at least 65 times the systemic drug exposure seen in humans treated with 1 drop into each eye of bimatoprost ophthalmic solution 0.03% once daily for 2 weeks. (Human dose calculated as 21 µg in a 35 µL drop dosed once daily in both eyes - not based on the 28 µL drop size as used in the Phase III studies.)

Two additional long term toxicity studies (1 month, 6 months duration) were performed in rabbits to support the bimatoprost ophthalmic solution 0.01% formulation containing benzalkonium chloride at a concentration of 0.2 mg/mL.

The observations in the 1-month ocular toxicity study in female New Zealand White rabbits included mild conjunctival hyperaemia and mild corneal degeneration and regeneration with all formulations (including placebo vehicle) containing 0.2 mg/mL benzalkonium chloride and 0%, 0.015% or 0.02% bimatoprost, suggesting that corneal epithelial alterations were benzalkonium chloride-induced. In the 6-month ocular toxicity study in male and female Dutch Belted rabbits, there were no indications of general or ocular toxicity related to ocular dosing of either bimatoprost ophthalmic solution 0.01% with 0.2 mg/mL benzalkonium chloride or bimatoprost ophthalmic solution 0.0125% with 0.2 mg/mL benzalkonium chloride, when administered up to three times daily over a 6-month period to Dutch Belted rabbits.

No effects were observed in mice given 4 mg/kg/day bimatoprost orally for 3 months. This dose achieved systemic exposure that was 149 times higher than that observed in humans treated with bimatoprost ophthalmic solution 0.03% with 0.05 mg/mL benzalkonium chloride, one drop/day in both eyes for 14 days. Female mice given oral doses of 8 mg/kg/day showed a reversible thymic lymphoid proliferation. This effect was observed only in mice and at a dose 460-fold higher than that observed in humans given bimatoprost ophthalmic solution 0.03% with 0.05 mg/mL benzalkonium chloride, one drop/day in both eyes for 14 days.

Increased aspartate aminotransferase and alanine aminotransferase (2- to 5-fold in males) was observed in rats given 8 or 16 mg/kg/day orally for 13 weeks. These changes were reversible after 4 weeks without treatment and no microscopic correlate was observed. In addition, increased ovarian weight and increased number of prominent, vacuolated corpora lutea were observed with these doses and with the dose of 4 mg/kg/day. Ovarian changes were also reversible at 4 weeks. The effects on the ovaries could be related to the pharmacological effect of this class drug in rats since these changes were not observed in other species. A dose of 4 mg/kg/day achieved systemic exposure that was 1538 times higher than that observed in humans treated with 1 drop into each eye of bimatoprost ophthalmic solution 0.03% once daily for 2 weeks.

A slight, reversible increase in alanine aminotransferase and aspartate aminotransferase was observed in rats given ≥ 0.1 mg/kg/day orally for 1 year. There were no associated microscopic liver findings. A dose-related, reversible cellular vacuolation of corpora lutea at ≥ 0.3 mg/kg/day in female rats was observed. The lowest effect dose of 0.1 mg/kg/day achieved systemic

exposure (C_{max}) that was 8 times higher than that observed in humans treated with bimatoprost ophthalmic solution 0.03% with 0.05 mg/mL benzalkonium chloride, one drop/day in both eyes for 14 days. Hepatic and ovarian effects in rats were considered species-specific since these changes have not been observed in mice and monkeys at systemic exposures up to 2,800- to 14,000-fold higher, respectively, than those in humans given bimatoprost ophthalmic solution 0.03% with 0.05 mg/mL benzalkonium chloride, one drop/day in both eyes for 14 days.

No treatment related systemic effects were produced when monkeys were intravenously administered from 0.01 to 1.0 mg/kg/day bimatoprost for 17 weeks. An increase in the prominence of the periocular sulci and widening of the palpebral fissure of both eyes were observed in all treated monkeys. This finding was reversible at 12 weeks after cessation of treatment. A dose of 0.01 mg/kg/day achieved systemic exposure that was 235 times greater than that observed in humans treated with 1 drop into each eye of bimatoprost ophthalmic solution 0.03% once daily for 2 weeks.

Mutagenicity

Bimatoprost was not mutagenic or clastogenic in a series of *in vitro* and *in vivo* studies (Ames test, Mouse Lymphoma and Micronucleus tests).

Salmonella/Escherichia Coli Mutagenicity Assay
Bimatoprost was tested in the bacterial reverse mutation assay (Ames assay) using *S. typhimurium* tester strains TA98, TA100, TA 1535, and TA1537 and E. coli tester strains WP2 uvrA (pKM101) and WP2 (pKM101) in the presence and absence of Aroclor-induced rat liver S9. No positive response was observed in the mutagenicity assay at concentrations of up to 5000 µg per plate.

Mouse Lymphoma Mutagenesis Assay
Bimatoprost was tested in the reduced volume L5178Y/TK+/- mouse lymphoma mutagenesis assay in the presence and absence of Aroclor-induced rat liver S9, and was negative when tested at concentrations up to 900 µg/mL with or without S9.

In vivo Mouse Micronucleus Assay
Bimatoprost was assayed for clastogenic activity and potential to disrupt the mitotic apparatus by evaluating micronuclei in polychromatic erythrocyte (PCE) cells in mouse bone marrow. Bimatoprost is considered negative in the mouse bone marrow micronucleus test following 20 mg/kg/day in mice. The high dose was based on the limit of solubility.

Carcinogenicity

Bimatoprost was not carcinogenic when administered once daily orally (by gavage) at doses of 0.3, 1.0 and 2.0 mg/kg/day to mice and 0.1, 0.3 and 1.0 mg/kg/day to rats (192 or 291 times the human exposure based on blood AUC levels from subjects given bimatoprost ophthalmic

solution 0.03% with 0.05 mg/mL benzalkonium chloride, one drop/day in both eyes for 14 days) for 104 weeks.

Reproduction and Teratology

Impairment of Fertility
No impairment of fertility occurred in rats when males were treated for 70 days prior to cohabitation and females were treated for 15 days prior to mating. Treatment was continued in males until copulation was observed and in females through gestation day 7. The highest dose (0.6 mg/kg/day) achieved systemic exposure that was 103 times that observed in humans treated with 1 drop of bimatoprost ophthalmic solution 0.03% in each eye once daily for 2 weeks.

Pregnancy/Teratogenic Effects
Bimatoprost given orally at doses up to 0.3 or 0.6 mg/kg/day to pregnant rats during gestation day 7 through 17 caused abortion but no drug-related developmental effects. This effect was also seen in mice receiving 0.3 mg/kg/day during gestation day 6 through 15. The maternal no-observable-adverse-effect level (NOAEL) of bimatoprost was 0.1 or 0.3 mg/kg/day for mice or rats, respectively. Abortion was expected as a rodent-specific pharmacological effect. The lowest effect dose of 0.3 mg/kg in mice and rats achieved systemic exposure (AUC) that was at least 33 or 97 times higher respectively, than that observed in humans treated with bimatoprost ophthalmic solution 0.03% with 0.05 mg/mL benzalkonium chloride, one drop/day in both eyes for 14 days.

Perinatal and Postnatal
Treatment of F0 female rats given 0.3 mg/kg/day (at systemic exposure estimated at 41 times that observed in humans treated with bimatoprost ophthalmic solution 0.03% with 0.05 mg/mL benzalkonium chloride, one drop/day in both eyes for 14 days) or greater caused maternal toxicity as evidenced by reduced gestation length, increased late resorption, fetal death, and postnatal mortality and reduced pup body weight (a rodent-specific pharmacological effect). No effects on postnatal development and mating performance of the F1 offspring were observed in groups treated with dosages as high as 0.1 mg/kg/day. Neurobehavioral function, Caesarean-sectioning parameters, and litter parameters in F1 rats were unaffected by doses as high as 0.3 mg/kg/day.

Animal Lactation
In animal studies, bimatoprost has been shown to be excreted in breast milk.

Special Toxicity Studies

Bimatoprost did not possess antigenic, cutaneous or systemic anaphylactic potential, or produce dermal contact hypersensitivity responses when administered topically, intradermally or systemically in rodents and guinea pigs.

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READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

LUMIGAN® PF
Bimatoprost Ophthalmic Solution
(preservative free)

Read this carefully before you start using LUMIGAN PF 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 LUMIGAN PF.

What is LUMIGAN PF used for?
LUMIGAN PF eye drops are used to reduce high pressure in the eye in adult patients with open angle glaucoma or ocular hypertension. If the high pressure is not reduced, it could eventually damage your sight. Since **LUMIGAN PF** does not contain a preservative, it may be used in patients who could benefit from preservative-free drops.

How does LUMIGAN PF work?
LUMIGAN PF is an antiglaucoma preparation. It belongs to a group of medicines called prostamides. Your eye contains a clear, watery liquid that feeds the inside of the eye. Liquid is constantly being drained out of the eye and new liquid is made to replace this. If the liquid cannot drain out quickly enough, the pressure inside the eye builds up. **LUMIGAN PF** works by increasing the flow of liquid that is drained. This reduces the pressure inside the eye.

What are the ingredients in LUMIGAN PF?
Medicinal ingredients: Bimatoprost
Non-medicinal ingredients: Sodium chloride, sodium phosphate dibasic heptahydrate, citric acid monohydrate, and purified water. Sodium hydroxide and/or hydrochloric acid may be added to adjust pH.

LUMIGAN PF comes in the following dosage forms:
Ophthalmic solution, 0.03% w/v

Do not use LUMIGAN PF if:
- you are allergic to bimatoprost, to any of the other ingredients, or to any of the parts of the container (see section What are the ingredients)**.**

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

- are taking, or have recently taken, any other medicines. Using **LUMIGAN PF** with other medicines or other antiglaucoma products may redue their effectiveness.
- are pregnant or planning to become pregnant. You should ask your healthcare professional for advice before taking any medicine.
- are breastfeeding or planning to breastfeed. Ask your healthcare professional how to feed your baby while using **LUMIGAN PF**.
- have an active eye infection, inflammation (e.g. uveitis) or any other eye or eyelid condition.
- develop another eye condition (an injury or an infection).

- need to have eye surgery.
- have liver or kidney problems.

Other warnings you should know about:

Changes in Eye and Eyelid Color
LUMIGAN PF has been associated with iris pigmentation (change in the colored part of the eye). This is likely to be permanent. The change may be more noticeable if you are only treating one eye. Using too much **LUMIGAN PF** (overdose) may contribute to iris pigmentation. **LUMIGAN PF** use may also cause darkening of the eyelid skin which may be reversible in most patients.

Hair Growth
It is possible for hair growth to occur in areas of your skin that **LUMIGAN PF** frequently touches. Any excess solution that drips from the eye should be blotted with a tissue or other absorbent material to reduce the chance of this from happening. It is also possible for a difference in eyelash length, thickness, fullness, pigmentation, number of eyelash hairs, and/or direction of eyelash growth to occur between eyes. These differences, should they occur, will usually go away if you stop using **LUMIGAN PF**.

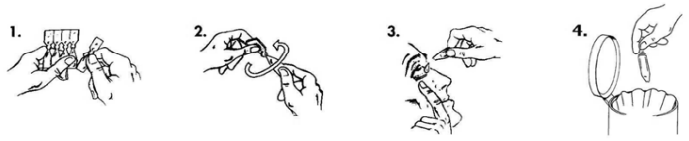
Changes in Vision
Using **LUMIGAN PF** may temporarily blur your vision. Do not drive or use machines until your vision has cleared.

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 LUMIGAN PF:
No drug interaction studies have been done with **LUMIGAN PF.**

How to use LUMIGAN PF:
- Always use **LUMIGAN PF** exactly as your healthcare professional has instructed you.
- Make sure the vial is not damaged before using it. If the vial is not intact, discard it.
- **LUMIGAN PF** must be used immediately after opening the vial.
- If you wear contact lenses, remove them before using **LUMIGAN PF**. Wait 15 minutes after using the drops before you put your lenses back in.
- If you use **LUMIGAN PF** with another eye drop, wait at least five minutes after using **LUMIGAN PF** before using the other drops.
- To help prevent infection, do not let the open end of the vial touch your eye or anything else.

Follow these steps to use **LUMIGAN PF** properly:
1. Wash your hands. Tear 1 vial from the strip. (See Illustration 1)
2. Hold the vial upright (with the cap pointing upwards) and twist off the cap. (See Illustration 2)
3. Gently pull down the lower eyelid to form a pocket. Turn the vial upside down and squeeze it to release 1 drop into the eyelid pocket. If a drop missed your eye, try again. (See Illustration 3)
4. Repeat stpes 1 – 3 in the other eye if both eyes need treatment.
5. Throw away the vial after you have used it, even if there is some solution left. (See Illustration 4)



Usual adult dose:
The recommended dosage is 1 drop of **LUMIGAN PF** in the each eye that needs treatment, once daily in the evening.

Overdose:

If you think you have used too much **LUMIGAN PF**, contact your healthcare practitioner, hospital emergency department or regional Poison Control Centre immediately, 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.

Missed Dose:
If you forget to take **LUMIGAN PF** use a single drop as soon as you remember, and then go back to your regular routine. Do not take two doses to make up for the one that you missed.

What are possible side effects from using LUMIGAN PF?

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

Side effects may include:

- Longer eyelashes, change in eyelash color
- Eye irritation, redness, itching, dryness
- Burning or stinging sensation in the eye
- Feeling that something is in your eye
- Eye pain
- Eye discharge
- Abnormal vision
- Red and itchy eyelids
- Darkening of the eyelid
- Inflammation of the eyelid
- Small breaks in the surface of the eye
- Sensitivity to light
- Tearing
- Tired eyes
- Dizziness
- Headache

Some patients (fewer than 2 in every 100) experience a change in iris color (iris pigmentation). The change is a darkening, with the eyes becoming more brown. This usually happens during the first year of treatment. Eye color darkening is expected to increase as long as **LUMIGAN PF** is used. It is not known what this change means over the long term. Talk to your healthcare professional if you notice a change in your iris color.

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.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:

LUMIGAN PF should be stored in the original container at 15ºC to 25ºC.

Do not use the drops after the expiry date stated on the single-dose container and the tray.

Once the tray is opened, the single-dose containers (vials) should be used within 30 days.

Keep out of the reach and the sight of children.

Do not freeze.

If you want more information about LUMIGAN PF:

• 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://www.canada.ca/en/health-canada.html); the manufacturer's website allergan.ca, or by calling 1-800-668-6424.

This leaflet was prepared by Allergan Inc.

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