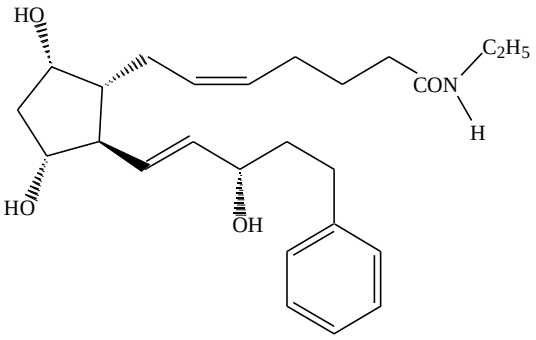
LUMIGAN® PF Eye Drops

NAME OF THE MEDICINE
The active constituent of LUMIGAN® PF eye drops is bimatoprost.
Chemical structure:



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

Molecular weight: 415.58

Empirical formula: $C_{25}H_{37}NO_4$

CAS Registry No.: 155206-00-1

DESCRIPTION
Bimatoprost (LUMIGAN® PF eye drops 300 mcg/mL) is a prostamide with potent ocular hypotensive activity. Bimatoprost is a white to off-white powder and is very soluble in ethyl alcohol and methyl alcohol and slightly soluble in water. LUMIGAN® PF is a clear, isotonic, colourless, sterile ophthalmic solution with an osmolality of approximately 290mOsmol/kg.

Composition:
LUMIGAN® PF 300 mcg/mL is a sterile ophthalmic solution in a single dose container. Each mL of LUMIGAN® PF solution contains:
ACTIVE: bimatoprost 300 microgram
INACTIVES: sodium phosphate dibasic; citric acid monohydrate; sodium chloride; and water - purified. Hydrochloric acid and/or sodium hydroxide may be added to adjust pH. Contains no antimicrobial agent.

PHARMACOLOGY
Pharmacotherapeutic group: Ophthalmolgicals; prostaglandin analogues; ATC code: S01EE03

Mechanism of action

Bimatoprost is a synthetic prostamide analogue with potent ocular hypotensive activity. It selectively mimics the effects of a newly discovered naturally occurring substance, prostamide. Prostamide is biosynthesised from anandamide by a pathway involving COX-2 but not COX-1, suggesting a new pathway that leads to the synthesis of endogenous lipid amides that lower intraocular pressure (IOP). Bimatoprost and prostamides differ from prostaglandins (PGs) in that prostamides are biosynthesised from a different precursor, anandamide; bimatoprost does not stimulate any previously described prostanoid receptor; it is not mitogenic; it does not contract the human uterus; and it is electrochemically neutral.

Bimatoprost reduces intraocular pressure in man by increasing aqueous humour outflow through the trabecular meshwork and enhancing uveoscleral outflow. Reduction of the intraocular pressure starts approximately 4 hours after the first administration and maximum effect is reached within approximately 8 to 12 hours. The duration of effect is maintained for at least 24 hours.

Clinical studies have shown mean intraocular pressure decreases of up to 9 mmHg.

Pharmacokinetics

Bimatoprost penetrates the human cornea and sclera *in vitro*.

After once daily ocular administration of one drop of LUMIGAN® 0.3 mg/mL (preserved multidose) to both eyes of 15 healthy subjects for two weeks, blood concentrations peaked within 10 minutes after dosing and declined to below the lower limit of detection (0.025 ng/mL) within 1.5 hours after dosing. Mean bimatoprost C_{max} values were similar on days 7 and 14 at 0.0721 and 0.0822 ng/mL respectively. The mean $AUC_{0\text{-}24hr}$ 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 was reached during the first week of ocular dosing. The systemic exposure of bimatoprost is very low with no accumulation over time.

Bimatoprost is moderately distributed into body tissues with a steady state systemic volume of distribution in humans of 0.67 L/kg. In human blood, bimatoprost resides mainly in the plasma. The plasma protein binding of bimatoprost is approximately 90%.

Data from *in vitro* studies showed that the overall extent of melanin binding was not dependent on concentration and the binding was reversible.

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

Bimatoprost is eliminated primarily by renal excretion. Up to 67% of an intravenous dose of radiolabeled bimatoprost administered to healthy volunteers was excreted in the urine, 25% of the dose was excreted via the faeces. The elimination half-life, determined after intravenous administration, was approximately 45 minutes, the total blood clearance of unchanged bimatoprost was 1.5 L/hr/kg.

After twice daily dosing, the mean $AUC_{0\text{-}24hr}$ value of 0.0634 ng.hr/mL for bimatoprost in the elderly (subjects 65 years or older) was statistically significantly higher than that of 0.0218 ng.hr/mL in young healthy adults, suggesting the existence of an age effect. However, this finding is not clinically relevant as systemic exposure for elderly and young subjects remained very low from ocular dosing. There was no accumulation of bimatoprost in the blood over time and the safety profile was similar in elderly and young patients.

CLINICAL TRIALS

Elevated IOP presents a major risk factor in the pathogenesis of glaucomatous visual field loss. The higher the level of intraocular pressure, the greater the likelihood of optic nerve damage and glaucomatous visual field loss. Bimatoprost has the action of lowering intraocular pressure with no clinically relevant effects on heart rate and blood pressure observed in clinical trials.

The efficacy of LUMIGAN® PF eye drops was demonstrated in a 12 week (double-masked, randomised, parallel group) clinical study comparing LUMIGAN® PF with LUMIGAN® (preserved multidose) once daily (evening) for 12 weeks in patients with glaucoma or ocular hypertension. Of the 596 patients treated, 301 received LUMIGAN® PF and 295 patients received LUMIGAN® (preserved multidose).

LUMIGAN® PF was considered to be non-inferior to LUMIGAN® (preserved multidose) 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® (preserved multidose)] did not exceed 1.5 mm Hg (as well as not exceeding 1.0 mm Hg) in the per protocol (PP) population. The upper limit did not exceed 0.75 mm Hg at any week 12 timepoint. Non-inferiority was also demonstrated for the intention to treat (ITT) population. Both treatments studied showed statistically and clinically significant mean decreases from baseline in worse eye IOP at all follow-up timepoints ($p < 0.001$).

Mean worse eye IOP changes from baseline ranged from -7.49 to -5.93 mm Hg for LUMIGAN® PF and -7.77 to -6.06 mm Hg for LUMIGAN® (preserved multidose) across weeks 2 to 12 for the PP population. The treatment differences [LUMIGAN® PF minus LUMIGAN® (preserved multidose)] in IOP change from baseline ranged from 0.02 to 0.37 mm Hg across the study (PP population).

LUMIGAN® PF was equivalent to LUMIGAN® (preserved multidose) with respect to average eye IOP at each follow-up timepoint at weeks 2, 6 and 12 (the upper limit of the 95% CI was ≤ 1.5 mm Hg and the lower limit was ≥ -1.5 mm Hg at the timepoint) for the ITT population. Furthermore, the upper limit of the 95% CI for treatment differences in average eye IOPs was ≤ 1.0 mm Hg and the lower limit is ≥ -1.0 mm Hg at all follow-up timepoints. In fact, at no timepoint was the lower limit of the 95% CI less than –0.50 mm Hg, or the upper limit above 0.69 mm Hg. The treatment differences in IOP ranged from -0.07 to 0.25 mm Hg across the study in the ITT population.

LUMIGAN® PF was considered equivalent to LUMIGAN® (preserved multidose) with respect to change from baseline in average eye IOP at each follow-up timepoint in both ITT and PP populations. Both treatments studied showed statistically and clinically significant mean decreases from baseline in average eye IOP at all follow-up timepoints ($p < 0.001$). Mean changes from baseline in average eye IOP ranged from -7.36 to -5.67 mm Hg for LUMIGAN® PF and from -7.50

to -5.70 mm Hg for LUMIGAN® (preserved multidose) across the study as measured on weeks 2, 6 and 12 (hours 0, 2 and 8) in the ITT population.

INDICATIONS

LUMIGAN® PF is indicated for the reduction of elevated intraocular pressure, or open angle glaucoma, as first line therapy or monotherapy or as adjunctive therapy to topical beta-blockers.

CONTRAINDICATIONS

LUMIGAN® PF eye drops are contraindicated in patients with significant hypersensitivity to bimatoprost or to any component of the medication.

PRECAUTIONS

General

LUMIGAN® PF has not been studied in patients with heart block more severe than first degree or uncontrolled congestive heart failure. There have been a limited number of spontaneous reports of bradycardia or hypotension with LUMIGAN® (preserved multidose) eye drops. LUMIGAN® PF should be used with caution in patients predisposed to low heart rate or low blood pressure.

LUMIGAN® PF has not been studied in patients with compromised respiratory function and should therefore be used with caution in such patients. In clinical studies, in those patients with a history of a compromised respiratory function, no significant untoward respiratory effects have been seen.

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

During treatment with bimatoprost, darkening of the eyelid skin and gradual increased eyelash growth (lengthening, darkening and thickening) with no consequent untoward ocular effects have been observed. Increased iris pigmentation has also been reported. The change in iris pigmentation occurs slowly and may not be noticeable for several months to years. Neither naevi nor freckles of the iris appear to be affected by treatment.The effect has been seen in up to 2% of patients treated with LUMIGAN® (preserved multidose) for up to 6 months. At 12 months, the incidence of iris pigmentation with LUMIGAN® (preserved multidose) was 1.5% and did not increase following 3 years treatment. At 3 months, the incidence of iris hyperpigmentation with LUMIGAN® PF dose was 0.3%. The long-term effects of increased iris pigmentation are not known.

Some of these changes may be permanent and may lead to differences in appearance between the eyes when only one eye is treated.

Periorbital tissue pigmentation has been reported to be reversible in some patients.
There is the potential for hair growth to occur in areas where LUMIGAN® PF solution comes repeatedly in contact with the skin surface. Thus, it is important to apply LUMIGAN® PF as instructed and to avoid it running onto the cheek or other skin areas.

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

Macular oedema, including cystoid macular oedema, has been reported during treatment with LUMIGAN® (multidose formulation) for elevated IOP. 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 oedema (e.g. intraocular surgery, retinal vein occlusions, ocular inflammatory disease and diabetic retinopathy).

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

In LUMIGAN® (preserved multidose) 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. Patients using LUMIGAN® PF with other prostaglandin analogs should be monitored for changes to their intraocular pressure.

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

LUMIGAN® PF has not been studied in patients wearing contact lenses.

Preclinical Findings:
Ocular administration of bimatoprost in monkeys at concentrations of ≥0.3 mg/mL once or twice daily for 1 year caused an increase in iris pigmentation and reversible dose-related periocular effects characterised by a prominent upper and/or lower sulcus and widening of the palpebral fissure. 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.

Periocular effects were also observed in an intravenous toxicity study at systemic exposures at least 235-fold higher than that observed in humans after ocular administration. No functional or microscopic changes related to the periocular effects were observed. The mechanism of action for the observed periocular changes is unknown.

Carcinogenicity:

Long-term studies in mice and rats revealed no evidence of carcinogenicity following oral (by gavage) administration of bimatoprost at doses up to 2 and 1 mg/kg/day, respectively. These doses resulted in systemic bimatoprost levels 85 – 95 times the maximum anticipated human exposure (based on blood AUC). In the rat carcinogenicity study, a dose-related increase in vacuolated corpora lutea was observed. The clinical relevance of this ovarian effect is unclear.

Genotoxicity:
Bimatoprost was not mutagenic or clastogenic in a bacterial mutation assay, in a mouse lymphoma test *in vitro* or in a mouse micronucleus test.

Effects on Fertility:
Bimatoprost did not affect fertility in male or female rats at oral doses up to 0.6 mg/kg/day corresponding to 30 – 50 times the expected human exposure (based on blood AUC calculated from total blood concentration).

Use in Pregnancy: Category B3

There are no adequate and well-controlled studies in pregnant women. Bimatoprost and/or its metabolites crossed the placenta in rats. In embryo/foetal developmental studies in pregnant mice and rats, abortion was observed at oral doses of bimatoprost of 0.3 and 0.6 mg/kg/day, respectively, resulting in exposures 15 and 34 times the expected human exposure (based on blood AUC calculated from total blood concentration). Bimatoprost was not teratogenic at up to 0.6 mg/kg/day in mice or rats. At doses of ≥ 0.3 mg/kg/day PO in rats, approximately 20 times the expected human exposure, the gestation length was reduced, embryofoetal losses and peri- and postnatal pup mortality were increased, and pup body weights were reduced.
LUMIGAN® PF should not be used during pregnancy unless clearly necessary.

Use in Lactation:

Bimatoprost was excreted in rat milk following PO administration. Increased pup mortality and depressed pup growth occurred when dams were treated PO with bimatoprost from gestation day 7 to lactation day 20 at ≥ 0.3 mg/kg/day, corresponding to exposures approximately 20 times the expected human exposure (based on blood AUC calculated from total blood concentration).

There are no data on the excretion of bimatoprost into human milk or on the safety of bimatoprost exposure in infants. Because many drugs are excreted in human milk, nursing women who use LUMIGAN® PF should stop breast feeding.

Paediatric Use:

Safety and effectiveness in patients below 18 years of age have not been established and therefore its use is not recommended.

Use in elderly:

No dosage adjustment in elderly patients is necessary.

Information for patients:

Based on the pharmacodynamic profile, bimatoprost is not expected to affect the ability to drive and use machines. 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.

Each ampoule is intended only for a single treatment in the affected eye(s). Discard any remaining solution in the ampoule immediately after use. LUMIGAN® PF has not been studied in patients wearing contact lenses.

INTERACTIONS WITH OTHER MEDICINES

No interaction studies have been performed.

No drug-drug interactions are anticipated in humans since systemic concentrations of bimatoprost are extremely low (less than 0.2 ng/mL) following ocular dosing with LUMIGAN® (preserved multidose). No effects on hepatic drug metabolising enzymes were observed in pre-clinical studies. Therefore, specific interaction studies with other medicinal products have not been performed with LUMIGAN® PF eye drops.

In clinical studies, LUMIGAN® (preserved multidose) was used concomitantly with a number of different ophthalmic beta-blocking agents without evidence of drug interactions.

Concomitant use of LUMIGAN® (preserved multidose) and anti-glaucoma 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 analog to be reduced in patients with glaucoma or ocular hypertension when used with other prostaglandin analogs.

ADVERSE EFFECTS

In a 3-month clinical study, approximately 29% of patients treated with LUMIGAN® PF 300 mcg/mL eye drops experienced adverse reactions. The most frequently reported adverse reactions were conjunctival hyperaemia (mostly trace to mild and of a non-inflammatory nature) occurring in 24% of patients, and eye pruritus occurring in 4% of patients. Approximately 0.7% of patients in the LUMIGAN® PF eye drop group discontinued due to any adverse event in the 3 month study.

A total of 302 and 295 patients were randomised to the LUMIGAN® PF and LUMIGAN® (preserved multidose) treatment groups, respectively. The following undesirable effects considered related to treatment were reported in ≥ 1% of patients during treatment with LUMIGAN® PF. Most were ocular, mild and none was serious.

Table 1 Summary of Adverse Reactions in ≥ 1% of Patients in the LUMIGAN® PF Treatment Group

System Organ Class Preferred Term	LUMIGAN® PF eye drops N= 301
Eye disorders	
Conjunctival hyperaemia	72 (23.9%)
Eye pruritus	12 (4.0%)
Punctate keratitis	9 (3.0%)
Foreign body sensation in eyes	7 (2.3%)
Dry eye	5 (1.7%)
Growth of eyelashes	5 (1.7%)
Eye pain	4 (1.3%)
Eye irritation	3 (1.0%)
Erythema of eyelid	3 (1.0%)
Skin and subcutaneous tissue disorders	
Skin hyperpigmentation	3 (1.0%)

The following undesirable effects definitely, probably or possibly related to treatment were reported during clinical trials or reported as postmarketing events with LUMIGAN®. Most were ocular, mild to moderate, and none was serious. No new adverse effects were observed in the LUMIGAN PF clinical study.

Eye disorders:
Very common (>10%): conjunctival hyperemia, growth of eyelashes, ocular pruritus.

Common (≥1% to < 10%): allergic conjunctivitis, asthenopia, blepharitis, conjunctival oedema, corneal erosion, eye discharge, eyelash darkening, eyelid erythema, eyelid pruritus, eye pain, foreign body sensation, increased iris pigmentation, ocular burning, ocular dryness, ocular irritation, photophobia, pigmentation of periocular skin, superficial punctate keratitis, tearing, visual disturbance and worsening of visual acuity.

Uncommon (<1%): blepharospasm, eyelid oedema, eyelid retraction, iritis, retinal hemorrhage.

Unknown: deepened lid sulcus (enophthalmos), erythema (periorbital), eyelid edema, macular edema

Gastrointestinal disorders
Unknown: nausea

General disorders and administration site conditions
Common: asthenia

Respiratory, thoracic and mediastinal disorders
Uncommon: infection (primarily colds and upper respiratory tract infections).

Nervous system disorders
Common: headache

Uncommon: depression, vertigo

Unknown: dizziness

Skin and subcutaneous disorders
Uncommon: hirsutism

Unknown: hair growth abnormal

Vascular disorders
Unknown: hypertension

Post Marketing experience:
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:

Respiratory, thoracic and mediastinal disorders:
Asthma, exacerbation of asthma, dyspnea

Immune system disorders
Hypersensitivity reaction including signs and symptoms of eye allergy and allergic dermatitis

DOSAGE AND ADMINISTRATION

Monotherapy: The recommended dose is one drop of LUMIGAN® PF in the affected eye(s) once daily, administered in the evening.

Adjunctive Therapy: The recommended dose is one drop of LUMIGAN® PF in the affected eye(s) once daily, administered in the evening.

More frequent administration has not been shown to provide increased efficacy.

If more than one topical ophthalmic medication is to be used, the other medication should not be used within 5 minutes of using LUMIGAN® PF eye drops.

In order to minimise systemic absorption of LUMIGAN® PF eye drops, patients should be instructed to apply pressure to the tear duct immediately following administration of the drug.

Each ampoule is intended for a single treatment in the affected eye(s). Discard the ampoule immediately after use.

OVERDOSAGE

No information is available on overdosage in humans; overdose is unlikely to occur after ocular administration.

If overdosage occurs, treatment should be symptomatic and supportive.
If LUMIGAN® PF eye drops are accidently ingested, the following information may be useful; 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 if they were to accidently ingest the entire contents of the package (30 unit dose ampoules with 0.4 mL per ampoule or 12 mL) of LUMIGAN® PF.

PRESENTATION AND STORAGE CONDITIONS
LUMIGAN® PF eye drops sterile solution is supplied in clear, single dose LDPE containers with a twist off tab. Each single-dose container contains 0.4 mL solution. The following pack sizes are available: 5 or 30 single-dose 0.4 mL containers.

LUMIGAN® PF eye drops have a shelf life of 18 months for the 30 x 0.4 mL pack and 9 months for the 5 x 0.4 mL pack. For the 30 x 0.4 mL pack once the tray is opened, the ampoules should be used within 30 days.Store below 25°C.

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NAME AND ADDRESS OF THE SPONSOR
Allergan Australia Pty Ltd
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Poison Schedule of the Medicine: S4, prescription only medicine

Date of first inclusion in the Australian Register of Therapeutic Goods:
15th May 2013
Date of the most recent amendment: 11th July 2016
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