

AUSTRALIAN PRODUCT INFORMATION

LUMIGAN[®] PF (BIMATOPROST) EYE DROPS

1 NAME OF THE MEDICINE

Bimatoprost

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

LUMIGAN[®] PF eye drops contains bimatoprost 300 micrograms/mL

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Eye drops, solution

LUMIGAN[®] PF eye drops is a clear, isotonic, colourless, sterile ophthalmic solution with an osmolality of approximately 290 mOsmol/kg.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

LUMIGAN[®] PF eye drops 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.

4.2 DOSE AND METHOD OF ADMINISTRATION

Monotherapy:

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

Adjunctive Therapy:

The recommended dose is one drop of LUMIGAN[®] PF eye drops 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.

4.3 CONTRAINDICATIONS

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

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

General:

LUMIGAN[®] PF eye drops 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 eye drops should be used with caution in patients predisposed to low heart rate or low blood pressure.

LUMIGAN[®] PF eye drops 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.

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) eye drops for up to 6 months. At 12 months, the incidence of iris pigmentation with LUMIGAN[®] (preserved multidose) eye drops was 1.5% and did not increase following 3 years treatment. At 3 months, the incidence of iris hyperpigmentation with LUMIGAN[®] PF eye drops 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 eye drops solution comes repeatedly in contact with the skin surface. Thus, it is important to apply

LUMIGAN® PF eye drops as instructed and to avoid it running onto the cheek or other skin areas.

LUMIGAN® PF eye drops 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® (preserved multidose) eye drops for elevated IOP. LUMIGAN® PF eye drops 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 eye drops 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) eye drops 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 eye drops with other prostaglandin analogues 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.

Use in hepatic impairment

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

Use in renal impairment

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

Use in the elderly

No dose adjustment in elderly patients is necessary.

Paediatric use

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

Information for patients:

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 eye drops has not been studied in patients wearing contact lenses.

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

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) eye drops. 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) eye drops was used concomitantly with a number of different ophthalmic beta-blocking agents without evidence of drug interactions.

Concomitant use of LUMIGAN[®] (preserved multidose) eye drops 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 analogues to be reduced in patients with glaucoma or ocular hypertension when used with other prostaglandin analogues.

4.6 FERTILITY, PREGNANCY AND LACTATION**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

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 embryofetal 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, embryofetal losses and peri- and postnatal pup mortality were increased, and pup body weights were reduced. LUMIGAN[®] PF eye drops 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 eye drops should stop breast feeding.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

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.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

In a 3-month clinical study, approximately 29% of patients treated with LUMIGAN[®] PF 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) eye drops treatment groups, respectively. The following undesirable effects considered related to treatment were reported in $\geq 1\%$ of patients during treatment with LUMIGAN[®] PF eye drops. Most were ocular, mild and none were serious.

Table 1 Summary of Adverse Reactions in $\geq 1\%$ 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 post-marketing events with LUMIGAN[®] (preserved multidose) eye drops. Most were ocular, mild to moderate, and none was serious. No new adverse effects were observed in the LUMIGAN[®] PF eye drops clinical study.

Eye disorders:

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

Common ($\geq 1\%$ 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

Nervous system disorders:

Common: headache

Uncommon: depression, vertigo

Unknown: dizziness

Respiratory, thoracic and mediastinal disorders:

Uncommon: infection (primarily colds and upper respiratory tract infections)

Skin and subcutaneous tissue disorders:

Uncommon: hirsutism

Unknown: hair growth abnormal

Vascular disorders:

Unknown: hypertension

Gastrointestinal disorders:

Unknown: nausea

General disorders and administration site conditions:

Common: asthenia

Post-marketing experiences:

The following adverse reactions have been identified during post-marketing use of LUMIGAN® PF eye drops. Because post-marketing 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

Respiratory, thoracic and mediastinal disorders:

Asthma, exacerbation of asthma, dyspnoea

Vascular disorders:

Hypertension

Nervous system disorders:

Dizziness

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product.

Healthcare professionals are asked to report any suspected adverse reactions at

www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

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

If overdose occurs, treatment should be symptomatic and supportive.

If LUMIGAN® PF eye drops are accidentally 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/m² is at least 32-times higher than the amount of bimatoprost to which a 10 kg child would be exposed if they were to accidentally ingest the entire contents of the package (30 unit dose ampoules with 0.4 mL per ampoule or 12 mL) of LUMIGAN® PF eye drops.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: anti-glaucoma preparation; prostaglandin analogues; *ATC code:* S01EE03

5.1 PHARMACODYNAMIC PROPERTIES

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.

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 eye drops with LUMIGAN[®] (preserved multidose) eye drops once daily (evening) for 12 weeks in patients with glaucoma or ocular hypertension. Of the 596 patients treated, 301 received LUMIGAN[®] PF eye drops and 295 patients received LUMIGAN[®] (preserved multidose) eye drops.

LUMIGAN[®] PF eye drops was considered to be non-inferior to LUMIGAN[®] (preserved multidose) eye drops 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 mmHg (as well as not exceeding 1.0 mmHg) in the per protocol (PP) population. The upper limit did not exceed 0.75 mmHg 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 mmHg for LUMIGAN[®] PF eye drops and 7.77 to 6.06 mmHg for LUMIGAN[®] (preserved multidose) eye drops 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 mmHg across the study (PP population).

LUMIGAN[®] PF eye drops was equivalent to LUMIGAN[®] (preserved multidose) eye drops 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 mmHg and the lower limit was ≥ 1.5 mmHg 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 mmHg and the lower limit is ≥ 1.0 mmHg at all follow-up timepoints. In fact, at no timepoint was the lower limit of the 95% CI less than -0.50 mmHg, or the upper limit above 0.69 mmHg. The treatment differences in IOP ranged from -0.07 to 0.25 mmHg across the study in the ITT population.

LUMIGAN[®] PF eye drops was considered equivalent to LUMIGAN[®] (preserved multidose) eye drops 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 mmHg for LUMIGAN[®] PF eye drops and from 7.50 to 5.70 mmHg for LUMIGAN[®] (preserved multidose) eye drops across the study as measured on weeks 2, 6 and 12 (hours 0, 2 and 8) in the ITT population.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

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

After once daily ocular administration of one drop of LUMIGAN® 300 micrograms/mL (preserved multidose) eye drops 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_{0-24hr} 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.

Distribution

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.

Metabolism

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.

Excretion

Bimatoprost is eliminated primarily by renal excretion. Up to 67% of an intravenous dose of radiolabelled 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_{0-24hr} 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.

5.3 PRECLINICAL SAFETY DATA

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.

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.

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.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Preservative: Contains no antimicrobial agent.

Inactives: dibasic sodium phosphate heptahydrate; citric acid monohydrate; sodium chloride; and purified water. Hydrochloric acid and/or sodium hydroxide may be added to adjust pH.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C.

6.5 NATURE AND CONTENTS OF CONTAINER

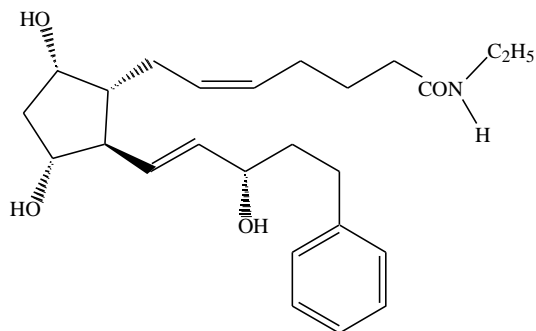
LUMIGAN[®] PF eye drops sterile solution is supplied in clear, single dose LDPE containers with a twist off tab. Each single-dose container contains 0.4 mL solution. The following pack sizes are available: 5 or 30 single-dose 0.4 mL containers.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking it to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

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: C₂₅H₃₇NO₄

CAS number: 155206-00-1

Description:

Bimatoprost is a white to off-white powder and is very soluble in ethyl alcohol and methyl alcohol and slightly soluble in water.

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4: Prescription Only Medicine

AUST R 199469

8 SPONSOR

Allergan Australia Pty Ltd
810 Pacific Highway
Gordon NSW 2072
ABN: 85 000 612 831

9 DATE OF FIRST APPROVAL

15 May 2013

10 DATE OF REVISION

24 January 2019

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SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
	The PI has been reformatted in line with the TGA's approved form for PIs. Additional mandatory headings and standard text have been included to the PI line with the TGA's approved form for PIs.
4.8	Additional Post-marketing Adverse Effects have been included under the sub-headings "Eye disorders", "Nervous system disorders" and "Vascular disorders", in line with CCDS v11.0.
5	The "Pharmacotherapeutic group" has been amended in line with CCD v11.0
6.1	Excipient names have been updated in line with the TGA's Updated Medicine