NEW ZEALAND DATA SHEET

1. PRODUCT NAME

LUMIGAN® PF (bimatoprost) 0.3 mg/mL eye drops

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

LUMIGAN® PF eye drops contains bimatoprost 0.3 mg/mL

For full list of excipients, see section 6.1 List of Excipients.

3. PHARMACEUTICAL FORM

LUMIGAN® PF (bimatoprost) eye drops are a clear, isotonic, colourless, sterile ophthalmic solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

LUMIGAN® PF is indicated as monotherapy for the reduction of elevated intraocular pressure (IOP) in patients with chronic glaucoma or ocular hypertension; or as adjunctive therapy in patients not adequately controlled on other agents.

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.
For single use only, one container is sufficient to treat both eyes. Any unused solution should be discarded immediately after use.

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.

4.3 Contraindications

LUMIGAN® PF eye drops are contraindicated in patients with 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® (preserved multidose) 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.

LUMIGAN® PF eye drops 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.

Before treatment is initiated, patients should be informed of the possibility of prostaglandin analogue periorbitopathy (PAP) and increased iris pigmentation. Some of these changes may be permanent and may lead to impaired field of vision and differences in appearance between the eyes when only one eye is treated (see Section 4.8 Undesirable effects).

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

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.

4.5 Interaction 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. 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 antiglaucoma 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.

4.6 Fertility, pregnancy and lactation

Impairment of Fertility:

Bimatoprost did not affect fertility in male or female rats at oral doses up to 0.6 mg/kg/day (approximately 103 times the intended human exposure).

Pregnancy and Lactation:

Pregnancy Category B3

In embryo/ foetal development studies in pregnant mice and rats abortion but no developmental effects were observed at doses that were at least 33 or 97 times higher, respectively, than the intended human exposure. In peri/postnatal studies in rats, reduced gestation time, foetal death and decreased pup body weights were observed in dams given ≥ 0.3 mg/kg/day (a rodent-specific pharmacological effect; systemic exposure estimated to be at least 41 times the intended human exposure). This maternal toxicity likely resulted in decreased mating performance and gestational body weight gain in the offspring, but neurobehavioural functions were not affected.

There are no adequate and well-controlled studies in pregnant women. 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 41 times the expected human exposure.

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 Undesirable effects

In a 3-month clinical study, approximately 29% of patients treated with LUMIGAN® PF 0.03 mg/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 eye drops. 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® 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 (≥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:

Eye disorders:
Eye discharge, ocular discomfort, prostaglandi analogue periorbitopathy,

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

Vascular disorders:
Hypertension

Nervous system disorders:
Dizziness

Description of selected adverse reactions:

Prostaglandin analogue periorbitopathy (PAP)

Prostaglandin analogues including LUMIGAN PF can induce periorbital lipodystrophic changes which can lead to deepening of the eyelid sulcus, ptosis, enophthalmos, eyelid retraction, involution of dermatochalasis and inferior scleral show. Changes are typically mild, can occur as early as one month after initiation of treatment with LUMIGAN PF, and may cause impaired field of vision even in the absence of patient recognition. PAP is also associated with periocular skin hyperpigmentation or discoloration and hypertrichosis. All changes have been noted to be partially or fully reversible upon discontinuation or switch to alternative treatments.

Iris hyperpigmentation

Increased iris pigmentation is likely to be permanent. The pigmentation change is due to increased melanin content in the melanocytes rather than to an increase in the number of melanocytes. The long-term effects of increased iris pigmentation are not known. Iris colour changes seen with ophthalmic administration of bimatoprost may not be noticeable for several months to years. Typically, the brown pigmentation around the pupil spreads concentrically towards the periphery of the iris and the entire iris or parts become more brownish. Neither naevi nor freckles of the iris appear to be affected by the treatment. At 12 months, the incidence of iris hyperpigmentation with bimatoprost 0.1 mg/ml eye drops, solution was 0.5%. At 12 months, the incidence with bimatoprost 0.3 mg/ml eye drops, solution was 1.5% and did not increase following 3 years treatment.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/.

4.9 Overdose

If overdose occurs, treatment should be symptomatic and supportive.
Ophthalmic overdose: No case of overdose has been reported, and is unlikely to occur after ocular administration.

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 eye drops.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5 PHARMACOLOGICAL PROPERTIES

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

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiglaucoma preparations; 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 biosynthesized 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 humor 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 efficacy and safety

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 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 intention to treat (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.

5.2 Pharmacokinetic properties

Bimatoprost penetrates the human cornea and sclera *in vitro*.
After once daily ocular administration of one drop of 0.03% bimatoprost 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 0.096ng.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 dependant 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 $AUC_{0\text{-}24hr}$ 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.

5.3 Preclinical safety dataFindings:

Ocular administration of bimatoprost in monkeys at concentrations of 0.03% or 0.1% 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

The carcinogenic potential of orally administered (gavage) bimatoprost was evaluated in mice given 0.3, 1.0 or 2.0 mg/kg/day and in rats given 0.1, 0.3 or 1.0 mg/kg/day for 104 weeks. There was no evidence of tumorigenic potential at any of the administered dosages in either species. In the rat carcinogenicity study, a dose-related increase in vacuolated corpora lutea was observed. The ovarian effects in rats is believed to be species specific.

Mutagenicity:

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

Not applicable

6.3 Shelf life

18 months for the 30 x 0.4 mL pack and 12 months for the 5 x 0.4 mL pack.

6.4 Special precautions for storage

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.

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

No special requirements for disposal.

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

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NEW ZEALAND
PH: 0800 900 030

9. DATE OF FIRST APPROVAL

24 October 2013

10. DATE OF REVISION OF TEXT

03 May 2023

SUMMARY TABLE OF CHANGES

Sections changed	Summary of new information
8. Sponsor	Updated sponsor details.