abbvie

LUMIGAN® PF 0.03%
(bimatoprost ophthalmic solution)

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use **LUMIGAN® PF** 0.03% (bimatoprost 0.03% preservative-free (PF) ophthalmic solution) safely and effectively. See full prescribing information for

LUMIGAN® PF 0.03% (bimatoprost ophthalmic solution)

----------INDICATIONS AND USAGE----------

LUMIGAN® PF 0.03% is a prostaglandin analog indicated for the reduction of elevated intraocular pressure in patients with open angle glaucoma or ocular hypertension. (1)

----------DOSAGE AND ADMINISTRATION----------

One drop in the affected eye(s) once daily in the evening. (2)

----------DOSAGE FORMS AND STRENGTHS----------

Solution containing 0.3 mg/mL bimatoprost. (3)

----------WARNINGS AND PRECAUTIONS----------

• Pigmentation.

Pigmentation of the iris, periorbital tissue (eyelid) and eyelashes can occur (5.1). Iris pigmentation likely to be permanent.

• Eyelash Changes.

Gradual change to eyelashes including increased length, thickness and number of lashes. Usually reversible. (5.2)

----------ADVERSE REACTIONS----------

Most common adverse reaction (23.9%) is conjunctival hyperemia. (6.1)

----------USE IN SPECIFIC POPULATIONS ----------

Use in pediatric patients has not been evaluated and therefore use is not recommended in children or adolescents. (7.3)

See 16 for Patient Counseling Information.

FULL PRESCRIBING INFORMATION: Contents*

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

LUMIGAN® PF 0.03% (bimatoprost ophthalmic solution) is indicated for the reduction of elevated intraocular pressure in patients with open angle glaucoma or ocular hypertension.

2 DOSAGE AND ADMINISTRATION

The recommended dosage is one drop in the affected eye(s) once daily in the evening. **LUMIGAN®** PF 0.03% (bimatoprost ophthalmic solution) should not be administered more than once daily since it has been shown that more frequent administration of prostaglandin analogs may decrease the intraocular pressure lowering effect.

Reduction of the intraocular pressure starts approximately 4 hours after the first administration with maximum effect reached within approximately 8 to 12 hours.

LUMIGAN® PF 0.03% may be used concomitantly with other topical ophthalmic drug products to lower intraocular pressure. If more than one topical ophthalmic drug is being used, the drugs should be

administered at least five (5) minutes apart.

3 DOSAGE FORMS AND STRENGTHS

Ophthalmic solution containing bimatoprost 0.3 mg/mL.

4 CONTRAINDICATIONS

LUMIGAN® PF 0.03% is contraindicated in patients with clinically significant hypersensitivity to bimatoprost or to any of the excipients.

5 WARNINGS AND PRECAUTIONS

Each vial is intended only for a single treatment in the affected eye(s). Discard vial immediately after use.
LUMIGAN® PF 0.03% has not been studied in patients wearing contact lenses.

5.1 Pigmentation

Bimatoprost ophthalmic solution has been reported to cause changes to pigmented tissues. The most frequently reported changes have been increased pigmentation of the iris, periorbital tissue (eyelid) and eyelashes. Pigmentation is expected to increase as long as bimatoprost is administered. The pigmentation change is due to increased melanin content in the melanocytes rather than to an increase in the number of melanocytes. After discontinuation of bimatoprost, pigmentation of the iris is likely to be permanent, while pigmentation of the periorbital tissue and eyelash changes have been reported to be reversible in some patients. Patients who receive treatment should be informed of the possibility of increased pigmentation. The long term effects of increased pigmentation are not known.

Iris color change 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 of the iris become more brownish. Neither nevi nor freckles of the iris appear to be affected by treatment. While treatment with **LUMIGAN®** PF 0.03% (bimatoprost ophthalmic solution) can be continued in patients who develop noticeably increased iris pigmentation, these patients should be examined regularly (see **PATIENT COUNSELING INFORMATION, 16.1**).

5.2 Eyelash Changes

LUMIGAN® PF 0.03% may gradually change eyelashes and vellus hair in the treated eye. These changes include increased length, thickness, and number of lashes. Eyelash changes are usually reversible upon discontinuation of treatment.

5.3 Intraocular Inflammation

LUMIGAN® PF 0.03% should be used with caution in patients with active intraocular inflammation (e.g., uveitis) because the inflammation may be exacerbated.

5.4 Macular Edema

Macular edema, including cystoid macular edema, has been reported during treatment with bimatoprost ophthalmic solution.

LUMIGAN® PF 0.03% 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).

5.5 Glaucoma

LUMIGAN® PF 0.03% has not been evaluated in patients with inflammatory ocular conditions, angle-closure, inflammatory or neovascular glaucoma, congenital glaucoma or narrow-angle glaucoma.

In **LUMIGAN®** 0.03% studies in patients with open angle 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®** with other prostaglandin analogs should be monitored for changes to their intraocular pressure.

5.6 Potential for Hair Growth

There is the potential for hair growth to occur in areas where **LUMIGAN®** PF 0.03% solution comes repeatedly in contact with the skin surface. Thus, it is important to apply **LUMIGAN®** PF 0.03% as instructed and to avoid it running onto the cheek or other skin areas.

5.7 Respiratory

LUMIGAN® PF 0.03% has not been studied in patients with compromised respiratory function and, therefore, should be used with caution in such patients. In clinical studies of **LUMIGAN®** 0.03%, in those patients with a history of a compromised respiratory function, no significant untoward respiratory effects have been seen.

6 ADVERSE REACTIONS

6.1 Clinical Studies Experience

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

In a clinical study with bimatoprost preservative free ophthalmic solution 0.03%, the most common adverse reaction was conjunctival hyperemia (23.9%).

Additional ocular adverse reactions (reported in 1 to 10% of patients) with bimatoprost preservative free ophthalmic solution 0.03% included eye pruritus, punctate keratitis, foreign body sensation in eyes, dry eye, growth of eyelashes, eye pain, erythema of eyelid, and eye irritation.

Other non-ocular adverse reactions (reported in 1 to 10%) included skin hyperpigmentation.

Approximately 0.7% of patients in the bimatoprost preservative free ophthalmic solution 0.03% group discontinued due to any adverse event in the 3 month study.

6.2 Postmarketing Experience

The following adverse reactions have been identified during postmarketing use of **LUMIGAN®** PF 0.03% in clinical practice. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. The events, which have been chosen for inclusion due to either their seriousness, frequency of reporting, possible causal connection to **LUMIGAN®** PF 0.03% or a combination of these factors, include:

Eye disorders

Eye discharge, Ocular discomfort, Periorbital and lid changes associated with periorbital fat atrophy and skin tightness resulting in deepening of eyelid sulcus, eyelid ptosis, enophthalmos and eyelid retraction

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

7 USE IN SPECIFIC POPULATIONS
7.1 Pregnancy
Pregnancy Category C

Teratogenic effects: In embryo/fetal developmental studies in pregnant mice and rats, abortion was observed at oral doses of bimatoprost which achieved at least 33 or 97 times, respectively, the maximum intended human exposure based on blood AUC levels.

At doses at least 41 times the maximum intended human exposure based on blood AUC levels, the gestation length was reduced in the dams, the incidence of dead fetuses, late resorptions, peri- and postnatal pup mortality was increased, and pup body weights were reduced.

There are no adequate and well-controlled studies of **LUMIGAN®** PF 0.03% (bimatoprost ophthalmic solution) administration in pregnant women. Because animal reproductive studies are not always predictive of human response, **LUMIGAN®** PF 0.03% should be administered during pregnancy only if the potential benefit justifies the potential risk to the fetus.

7.2 Nursing Mothers
It is not known whether **LUMIGAN®** PF 0.03% is excreted in human milk, although in animal studies, bimatoprost has been shown to be excreted in breast milk. Because many drugs are excreted in human milk, caution should be exercised when **LUMIGAN®** PF 0.03% is administered to a nursing woman.

7.3 Pediatric Use
Use in pediatric patients has not been evaluated and therefore use is not recommended in children or adolescents.

7.4 Geriatric Use
No overall clinical differences in safety or effectiveness have been observed between elderly and other adult patients.

7.5 Hepatic Impairment
LUMIGAN® PF 0.03% 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 ALT, AST and/or bilirubin at baseline, bimatoprost 0.03% had no adverse effect on liver function over 48 months.

8 DRUG INTERACTIONS
No interaction studies have been performed. There is a potential for the IOP-lowering effect of

prostaglandin analogs (e.g., **LUMIGAN®** PF 0.03%) to be reduced in patients with open angle glaucoma or ocular hypertension when used with other prostaglandin analogs (see **Warnings and Precautions, 5**).

9 OVERDOSAGE

No information is available on overdosage in humans. If overdose with **LUMIGAN®** PF 0.03% (bimatoprost ophthalmic solution) occurs, treatment should be symptomatic.

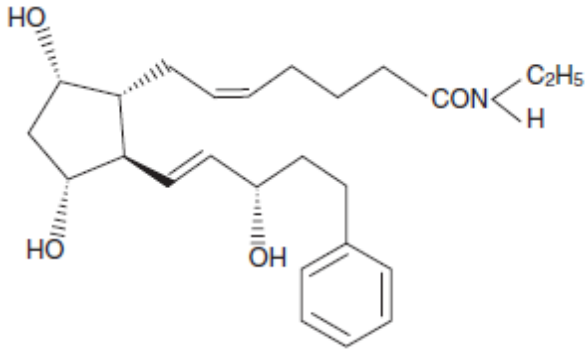
In short-term oral (by gavage) mouse and rat studies, doses up to 100 mg/kg/day did not produce any toxicity. This dose, expressed as mg/m^2, is at least 32 times higher than the amount of bimatoprost to which a 10 kg child would be exposed were it to accidentally ingest the entire content of a package (30 unit dose vials; 0.4 mL per vial; 12 mL total volume) of LUMIGAN® 0.03% (single dose).

10 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

As with any ocular treatment, if transient blurred vision occurs at instillation, the patient should wait until the vision clears before driving or using machinery.

11 DESCRIPTION

LUMIGAN® PF 0.03% (bimatoprost ophthalmic solution) is a synthetic prostaglandin analog with ocular hypotensive activity. Its chemical name is (Z)-7-[(1R,2R,3R,5S)-3,5-Dihydroxy-2-[(1E,3S)-3-hydroxy-5- phenyl-1-pentenyl]cyclopentyl]-5-N-ethylheptenamide, and its molecular weight is 415.58. Its molecular formula is $C_{25}H_{37}NO_4$. Its chemical structure is:



Bimatoprost is a powder, which is very soluble in ethyl alcohol and methyl alcohol and slightly soluble in water. **LUMIGAN®** PF 0.03% is a clear, isotonic, colorless, sterile ophthalmic solution with an osmolality of approximately 290 mOsmol/kg.

LUMIGAN® PF 0.03% in single dose container contains **Active**: bimatoprost 0.3mg/mL; **Inactives**: sodium chloride; sodium phosphate dibasic heptahydrate; citric acid monohydrate; and purified water. Sodium hydroxide and/or hydrochloric acid may be added to adjust pH. The pH during its shelf life ranges from 6.8-7.8.

12 CLINICAL PHARMACOLOGY

Pharmacotherapeutic group: Ophthalmologicals, prostaglandin analogues, ATC code: S01EE03.

12.1 Mechanism of Action

Bimatoprost, a prostaglandin analog, is a synthetic structural analog of prostaglandin with ocular hypotensive activity. It selectively mimics the effects of naturally occurring substances, prostamides. Bimatoprost is believed to lower intraocular pressure (IOP) in humans by increasing outflow of aqueous humor through both the trabecular meshwork and uveoscleral routes. Elevated IOP presents a major risk factor for glaucomatous

field loss. The higher the level of IOP, the greater the likelihood of optic nerve damage and visual field loss.

12.2 Pharmacokinetics

Absorption: After one drop of bimatoprost ophthalmic solution 0.03% was administered once daily to both eyes of 15 healthy subjects for two weeks, blood 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. Mean C_{max} and AUC_{0-24hr} values were similar on days 7 and 14 at approximately 0.08 ng/mL and 0.09 ng•hr/mL, respectively, indicating that steady state was reached during the first week of ocular dosing. There was no significant systemic drug accumulation over time.

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.

Elimination: Following an intravenous dose of radiolabeled 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.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Bimatoprost was not carcinogenic in either mice or rats when administered by oral gavage at doses of up to 2 mg/kg/day and 1 mg/kg/day respectively (at least 192 and 291 times the recommended human exposure based on blood AUC levels respectively) for 104 weeks.

Bimatoprost was not mutagenic or clastogenic in the Ames test, in the mouse lymphoma test, or in the *in vivo* mouse micronucleus tests.

Bimatoprost did not impair fertility in male or female rats up to doses of 0.6 mg/kg/day (at least 103 times the recommended human exposure based on blood AUC levels).

14 CLINICAL STUDIES

A double-masked, randomized, parallel group study compared the efficacy and safety of once-daily (evening) administration of Bimatoprost 0.03% PF (single dose, SD) with **LUMIGAN®** 0.03% (multidose) for 12 weeks in patients with glaucoma or ocular hypertension. Of the 596 patients treated, 301 received Bimatoprost 0.03% PF and 295 patients received **LUMIGAN®** 0.03%.

For the primary analysis, bimatoprost 0.03% SD was considered non-inferior to **LUMIGAN®** 0.03% 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 [bimatoprost 0.3 mg/ml SD minus **LUMIGAN®**] did not exceed 1.5 mm Hg (as well as not exceeding 1.0 mm Hg) in the Per-protocol (PP) population. In fact, the upper limit did not exceed 0.75 mm Hg at any week 12 timepoint. Non-inferiority was also demonstrated for the Intent-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 Bimatoprost 0.03% SD, and -7.77 to -6.06 mm Hg for **LUMIGAN®** across weeks 2 to 12 for the PP population. The treatment differences (bimatoprost 0.3 mg/mL SD minus **LUMIGAN®**) in IOP change from baseline ranged from 0.02 to 0.37 mm Hg across the study (PP population).

Bimatoprost 0.03% SD was equivalent to **LUMIGAN®** 0.03% 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.

Bimatoprost 0.03% SD was considered equivalent to **LUMIGAN®** 0.03% 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 bimatoprost 0.3 mg/mL SD, and from -7.50 to -5.70 mm Hg for **LUMIGAN®** 0.03% across the study as measured on weeks 2, 6 and 12 (hours 0, 2 and 8) in the ITT population.

15 HOW SUPPLIED/STORAGE AND HANDLING

LUMIGAN® PF 0.03% (bimatoprost ophthalmic solution) is supplied sterile in a 0.9 mL vial manufactured from LDPE. Each vial is filled to a volume of 0.4 mL.
The three pack sizes are:

- 10 x 0.4 mL single dose vials. Five single-dose vials are connected in a strip and two strips are packaged in a flow wrap pouch. One pouch is then placed in an outer carton.
- 30 x 0.4mL single dose vials. Five single-dose vials are connected in a strip and two strips are packaged in a flow wrap pouch. Three pouches are then placed in an outer carton.
- 90 x 0.4mL single dose vials. Five single-dose vials are connected in a strip and two strips are packaged in a flow wrap pouch. Nine pouches are then placed in an outer carton.

Not all pack sizes may be marketed

Storage: LUMIGAN® PF 0.03% should be stored below 30°C. Do not store in a refrigerator or freezer.
Discard the opened single-dose container immediately after use.

16 PATIENT COUNSELING INFORMATION

16.1 Potential for Pigmentation

Patients should be advised about the potential for increased brown pigmentation of the iris, which may be permanent. Patients should also be informed about the possibility of eyelid skin darkening, which may be reversible after discontinuation of **LUMIGAN®** PF 0.03% (bimatoprost ophthalmic solution).

16.2 Potential for Eyelash Changes

Patients should also be informed of the possibility of eyelash and vellus hair changes in the treated eye during treatment with **LUMIGAN®** PF 0.03%. These changes may result in a disparity between eyes in length, thickness, pigmentation, number of eyelashes or vellus hairs, and/or direction of eyelash growth.
Eyelash changes are usually reversible upon discontinuation of treatment. Before treatment is initiated, patients should be informed of the possibility of eyelash growth since this has been observed during

treatment with prostaglandin analogues, including **LUMIGAN®**.

16.3 Handling the Container

Patients should be instructed to avoid allowing the tip of the dispensing container to contact the eye, surrounding structures, fingers, or any other surface in order to avoid eye injury and contamination.

16.4 When to Seek Physician Advice

Patients should also be advised that if they develop an intercurrent ocular condition (e.g., trauma or infection), have ocular surgery, or develop any ocular reactions, particularly conjunctivitis and eyelid reactions, they should immediately seek their physician's advice concerning the continued use of **LUMIGAN®** PF 0.03%.

16.5 Use with Other Ophthalmic Drugs

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

Manufactured by:

Allergan Pharmaceuticals Ireland, Castlebar Road, Westport, County Mayo, Ireland

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CCDSv13

Date of Revision: 26 January 2024