PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PR**LUMIGAN RC®**

bimatoprost ophthalmic solution

Solution, 0.01% w/v, for ophthalmic use

Elevated Intraocular Pressure Therapy

Prostamide Analogue (ATC Code: S01EE03)

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

LUMIGAN RC® (bimatoprost) is indicated for:

- the reduction of elevated intraocular pressure in patients with open angle glaucoma or ocular hypertension

1.1 Pediatrics

Pediatrics (<18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

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

2 CONTRAINDICATIONS

- LUMIGAN RC is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

4 DOSAGE AND ADMINISTRATION

4.2 Recommended Dose and Dosage Adjustment

- The recommended dosage is one drop in the affected eye(s) once daily in the evening. The dosage of LUMIGAN RC should not exceed once daily since it has been shown that more frequent administration of bimatoprost ophthalmic solution may lessen the intraocular pressure (IOP) lowering effect and increase the frequency and severity of adverse events. See 7 WARNINGS AND PRECAUTIONS.

4.4 Administration

Patients should be instructed to avoid allowing the tip of the dispensing container to contact the eye or surrounding structures, to avoid eye injury and contamination of the solution.

LUMIGAN RC may be used concomitantly with other topical ophthalmic drug products to lower IOP. If more than one topical ophthalmic drug is being used, the drugs should be administered at least five (5) minutes apart.

Contact lenses should be removed prior to instillation of LUMIGAN RC and may be reinserted 15 minutes following its administration. See 7 WARNINGS AND PRECAUTIONS.

4.5 Missed Dose

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

5 OVERDOSAGE

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

In 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 210 times higher than the amount of bimatoprost to which a 10kg child would be exposed were it to accidentally ingest the contents of one 7.5 mL bottle of LUMIGAN RC.

For management of a suspected drug overdose, including accidental ingestion, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Ophthalmic	Solution, 0.01% w/v	Benzalkonium chloride 0.02 % w/v as preservative, citric acid monohydrate, purified water, sodium chloride, and sodium phosphate dibasic heptahydrate. Sodium hydroxide and/or hydrochloric acid may be added to adjust pH.

LUMIGAN RC is supplied sterile in white opaque plastic ophthalmic dispenser bottles in the following sizes: 3 mL (physician sample), 5 or 7.5 mL.

LUMIGAN RC is a clear, isotonic, buffered, preserved, colorless, sterile solution with a pH of 7.3 ± 0.5, and an osmolality of approximately 290 mOsmol/kg.

7 WARNINGS AND PRECAUTIONS

General

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

Bimatoprost ophthalmic solution may gradually change eye color, increasing the amount of brown pigment in the iris by increasing the number of melanosomes (pigment granules) in melanocytes. **The long-term effects on the melanocytes and the consequences of potential injury to the melanocytes and/or deposition of pigment granules to other area of the eye are currently unknown.** The change in iris color occurs slowly and may not be noticeable for several months to years. Pigmentation is expected to increase as long as bimatoprost ophthalmic solution is administered. In a 12-month clinical study, iris color change was reported in 0.5% of patients treated with bimatoprost ophthalmic solution 0.01%. Noticeable darkening of the iris has been reported in 1.5% of patients treated for 12 months with bimatoprost ophthalmic solution 0.03% at the proposed dose of one drop once daily in each affected eye (1.1% of patients treated for 6 months).

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

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

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

LUMIGAN RC contains benzalkonium chloride at a concentration of 0.02% (0.2 mg/mL), compared to 0.005% (0.05 mg/mL) in LUMIGAN®. Monitoring is required with frequent or prolonged use in dry eye patients or where the cornea is compromised.

There have been reports of bacterial keratitis associated with the use of multiple-dose containers of topical ophthalmic products. These containers had been inadvertently contaminated by patients who, in most cases, had a concurrent corneal disease or a disruption of the ocular epithelial surface. See Patient Medication Information.

Carcinogenesis and Mutagenesis

See 16 NON-CLINICAL TOXICOLOGY.

Driving and Operating Machinery

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

Hepatic/Biliary/Pancreatic

LUMIGAN RC has not been studied in patients with hepatic impairment and should therefore be used with caution in such patients.

Ophthalmologic

LUMIGAN RC should be used with caution in patients with active intraocular inflammation (e.g. uveitis).

Macular edema, including cystoid macular edema, has been reported during treatment with bimatoprost ophthalmic solution 0.03% for elevated IOP.

LUMIGAN RC should be used with caution in aphakic patients, in pseudophakic patients with a torn posterior lens capsule, or in patients with known risk factors for macular edema (e.g. intraocular surgery, retinal vein occlusions, ocular inflammatory disease and diabetic retinopathy).

LUMIGAN RC has not been adequately evaluated for the treatment of congenital, or narrow angle, angle-closure or neovascular glaucoma and inflammatory ocular conditions.

There is a potential for the IOP-lowering effect of prostaglandin analogs to be reduced in patients with glaucoma or ocular hypertension when used with other prostaglandin analogs.

In LUMIGAN 0.03% studies in patients with glaucoma or ocular hypertension, it has been shown that more frequent exposure of the eye to more than one dose of bimatoprost daily may decrease the IOP-lowering effect. Patients using LUMIGAN RC with other prostaglandin analogs should be monitored for changes to their IOP.

The pivotal clinical studies included patients with pseudoexfoliative and pigmentary glaucoma, in numbers proportionate to the population. All of these patients responded positively, however given the low absolute numbers of these patients enrolled no statistical significance can be concluded. None of these patients dropped out due to lack of efficacy or adverse experiences. LUMIGAN RC contains the preservative benzalkonium chloride, which may be absorbed by and cause discoloration of soft contact lenses. Patients wearing soft (hydrophilic) contact lenses should be instructed to remove contact lenses prior to administration of LUMIGAN RC and wait at least 15 minutes following administration before reinserting soft contact lenses.

The benzalkonium chloride concentration in LUMIGAN RC is 0.02% (0.2 mg/mL), compared to 0.005% (0.05 mg/mL) in LUMIGAN. Benzalkonium chloride, which is commonly used as a preservative in ophthalmic products, has been reported to cause punctate keratopathy and/or toxic ulcerative keratopathy. Therefore, monitoring is required with frequent or prolonged use in dry eye patients or where the cornea is compromised.

LUMIGAN RC has not been studied in patients with severe dry eye, and therefore, should not be used in patients with severe dry eye.

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

Renal

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

Reproductive Health: Female and Male Potential

- **Fertility**

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

7.1 Special Populations

7.1.1 Pregnant Women

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

There has been no experience of pregnancy during clinical trials.

In embryo/fetal developmental studies in pregnant mice and rats, abortion was observed at oral doses of bimatoprost that were at least 33 or 97 times, respectively, the intended human exposure (AUC) obtained in subjects administered bimatoprost ophthalmic solution 0.03%, one drop/day in both eyes for 14 days.

Maternal toxicity and reduced pup body weights were observed when female rats received oral doses that were at least 41 times the intended human exposure (AUC) obtained in subjects administered bimatoprost ophthalmic solution 0.03%, one drop/day in both eyes for 14 days). See 16 NON-CLINCAL TOXICOLOGY.

7.1.2 Breast-feeding

It is not known whether bimatoprost is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when LUMIGAN RC is administered to a nursing woman.

7.1.3 Pediatrics

Pediatrics (<18 years): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

7.1.4 Geriatrics

No overall clinical differences in safety or effectiveness have been observed between elderly and other adult patients. Use as directed for adult patients.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

In the 12-month multi-centre, double blind, active controlled clinical study with bimatoprost ophthalmic solution 0.01%, most adverse events were ocular, mild, and not serious. The most frequently reported adverse event was conjunctival hyperaemia (31.4% of patients treated).

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

The data presented below are taken from a randomized, multicentre, double-blind, parallel-group clinical study, of 12 months duration, which was conducted in 560 patients with glaucoma or ocular hypertension. Bimatoprost 0.01% solution was administered once daily and was compared to bimatoprost 0.03% and bimatoprost 0.0125% ophthalmic solutions administered once daily. Adverse events, coded using the COSTART dictionary available at the time of the study, regardless of causality, reported from this study are presented below in **Table 2**, using MedDRA System Organ Class, for LUMIGAN RC and LUMIGAN.

Table 2 – Number (%) of Patients with Ocular Adverse Events, Regardless of Causality, Reported by > 1% of Patients (Study 192024-031)

	LUMIGAN RC N = 185 (%)	LUMIGAN N = 187 (%)
All Ocular Events	88 (47.6%)[a]	116 (62.0%)
Eye disorders		
Ocular/conjunctival hyperaemia*	58 (31.4%)	73 (39.0%)
Erythema of eyelid*	7 (3.8%)	10 (5.3%)
Eye irritation*	7 (3.8%)	3 (1.6%)
Growth of eyelashes*	7 (3.8%)	6 (3.2%)
Conjunctival haemorrhage	5 (2.7%)	1 (0.5%)
Vision blurred*	5 (2.7%)	3 (1.6%)
Punctate keratitis*	4 (2.2%)	11 (5.9%)
Cataract	4 (2.2%)	4 (2.1%)
Eye pruritus*	4 (2.2%)	10 (5.3%)
Conjunctival oedema*	3 (1.6%)	1 (0.5%)
Visual acuity reduced	2 (1.1%)	4 (2.1%)
Eyelids pruritus*	2 (1.1%)	1 (0.5%)
Eye pain	2 (1.1%)	2 (1.1%)
Iris hyperpigmentation*	1 (0.5%)	2 (1.1%)
Vitreous floaters	2 (1.1%)	1 (0.5%)
Asthenopia*	1 (0.5%)	3 (1.6%)
Vitreous detachment	1 (0.5%)	3 (1.6%)
Lacrimation increased	1 (0.5%)	1 (0.5%)
Visual field defect	1 (0.5%)	2 (1.1%)
Foreign body sensation in eyes	0 (0.0%)	5 (2.7%)
Dry eye	0 (0.0%)	3 (1.6%)
Blepharitis	0 (0.0%)	3 (1.6%)
Abnormal sensation in eye	0 (0.0%)	3 (1.6%)
Eye allergy	0 (0.0%)	1 (0.5%)
Maculopathy	0 (0.0%)	2 (1.1%)

	LUMIGAN RC N = 185 (%)	LUMIGAN N = 187 (%)
Scotoma	0 (0.0%)	2 (1.1%)
Blepharitis allergic	0 (0.0%)	3 (1.6%)
Corneal erosion	0 (0.0%)	2 (1.1%)
Photophobia	0 (0.0%)	2 (1.1%)
General disorders and administration site conditions		
Instillation site irritation*	2 (1.1%)	1 (0.5%)
Infections and infestations		
Hordeolum	1 (0.5%)	2 (1.1%)
Investigations		
Intraocular pressure increased	0 (0.0%)	3 (1.6%)
Skin and subcutaneous tissue disorders		
Skin hyperpigmentation*	5 (2.7%)	10 (5.3%)
Hypertrichosis*[b]	3 (1.6%)	3 (1.6%)

Source: Report 192024-031, Tables 14.3-3.1 and 14.3-3.2, Table 14.3-4
* Event reported by an investigator as treatment-related for at least one patient for LUMIGAN RC.
a LUMIGAN RC significantly less than LUMIGAN ($p \leq 0.005$)
b Hypertrichosis reported as "hair growth around the eye"

Compared to LUMIGAN, LUMIGAN RC had significantly fewer adverse events (all causality and treatment-related), and significantly fewer ocular adverse events. Patients experienced less severe macroscopic hyperaemia.

Treatment related adverse events resulted in the discontinuation of 2.2% of patients on bimatoprost ophthalmic solution 0.01%, principally for conjunctival hyperaemia (1.6%). Of the patients treated with bimatoprost ophthalmic solution 0.03%, 6.4% discontinued as a result of a treatment related effect, principally for conjunctival hyperaemia (2.7%).

Non-Ocular Adverse Events

Table 3– Number (%) of Patients with Non-ocular Adverse Events, Regardless of Causality, Reported by > 1% of Patients treated with LUMIGAN RC (Study 192024-031)

	LUMIGAN RC N = 185 (%)	LUMIGAN N = 187 (%)
All non-ocular Events	80 (43.2%)	77 (41.2%)
Blood and lymphatic system disorders		
anaemia	3 (1.6%)	1 (0.5%)
Cardiac disorders		
cardiac failure congestive	3 (1.6%)	0 (0.0%)
chest pain	2 (1.1%)	2 (1.1%)
Endocrine disorders		
hypothyroidism	4 (2.2%)	1 (0.5%)
Gastrointestinal disorders		
gastrooesophageal reflux disease	6 (3.2%)	1 (0.5%)
nausea*	3 (1.6%)	1 (0.5%)
toothache	2 (1.1%)	0 (0.0%)
Infections and infestations		
upper respiratory tract infection	6 (3.2%)	3 (1.6%)
nasopharyngitis	5 (2.7%)	4 (2.1%)
pharyngitis streptococcal	3 (1.6%)	0 (0.0%)
influenza	2 (1.1%)	1 (0.5%)
urinary tract infection	2 (1.1%)	2 (1.1%)
Injury, poisoning & procedural complications		
skin laceration	3 (1.6%)	1 (0.5%)
procedural pain	2 (1.1%)	1 (0.5%)
fall	2 (1.1%)	2 (1.1%)
Metabolism and nutrition disorders		
hypercholesterolaemia	5 (2.7%)	5 (2.7%)
diabetes mellitus	5 (2.7%)	2 (1.1%)

	LUMIGAN RC N = 185 (%)	LUMIGAN N = 187 (%)
diabetes mellitus non-insulin dependent	3 (1.6%)	1 (0.5%)
dyslipidaemia	2 (1.1%)	0 (0.0%)
peripheral oedema	3 (1.6%)	2 (1.1%)
Musculoskeletal and connective tissue disorders		
muscle spasms	3 (1.6%)	0 (0.0%)
back pain	2 (1.1%)	6 (3.2%)
Nervous system disorders		
dizziness	3 (1.6%)	2 (1.1%)
headache*	3 (1.6%)	3 (1.6%)
Psychiatric disorders		
depression	3 (1.6%)	1 (0.5%)
Renal and urinary disorders		
nephrolithiasis	2 (1.1%)	0 (0.0%)
Respiratory, thoracic and mediastinal disorders		
cough	2 (1.1%)	1 (0.5%)
asthma	2 (1.1%)	3 (1.6%)
dyspnoea	2 (1.1%)	1 (0.5%)
bronchitis	2 (1.1%)	0 (0.0%)
nasopharyngitis	5 (2.7%)	4 (2.1%)
Vascular disorders		
hypertension	8 (4.3%)	11 (5.9%)
* Event reported by an investigator as treatment-related for at least one patient for LUMIGAN RC.		

8.3 Less Common Clinical Trial Adverse Reactions

The number of patients reporting an adverse event, regardless of causality, was 1 (0.5%) for each of the following adverse events:

Eye disorders: eyelid oedema*, eyelid pain, cataract nuclear, conjunctival disorder*, eyelid exfoliation, eyelid margin crusting*, keratoconjunctivitis sicca, meibomianitis, chalazion, chemical eye injury, conjunctivitis viral, corneal epithelium defect, corneal thinning, macular degeneration, macular hole, madarosis*, retinal pigment epitheliopathy, trichiasis
Immune system disorders: pruritus*

Infections and infestations: diverticulitis, pneumonia
Injury, poisoning & procedural complications: contusion
Musculoskeletal and connective tissue disorders: musculoskeletal pain
Psychiatric disorders: anxiety
Respiratory, thoracic and mediastinal disorders: sinusitis
Skin and subcutaneous tissue disorders: dry skin*, cellulitis

* Event reported by an investigator as treatment-related for LUMIGAN RC

Safety Data from Other Clinical Trials:

In double-blind, active-controlled clinical studies conducted with LUMIGAN once daily, the following treatment related adverse events were reported:

The frequency is defined as follows: Very Common (>10%); Common (≥1% to <10%); Uncommon (≥ 0.1% to <1%)

Cardiac disorders
Uncommon: chest pain, palpitations
Eye disorders
Very Common: conjunctival hyperaemia, growth of eyelashes, eye pruritus
Common: eye dryness, burning sensation in eye, blepharal pigmentation, foreign body sensation, eye pain, visual disturbance, erythema eyelid, eyelash discoloration, eye discharge, irritation eye, blepharitis, superficial punctuate keratitis, photophobia, allergic conjunctivitis, epiphora, iris pigmentation increased, visual acuity worsened, asthenopia, cataract NOS, conjunctival oedema
Uncommon: corneal erosion, stinging sensation eye, eyelid pruritus, blepharospasm, conjunctiva (NOS), eyelid oedema, chalazion, eye oedema, hordeolum, conjunctival bleb, conjunctival folliculosis, eyelid (NOS), eyelid pain, iritis (ocular inflammation), keratitis, visual field defect, vitreous floaters, diplopia
Gastrointestinal disorders
Uncommon: oral dryness, dyspepsia
General disorders and administration site conditions
Common: asthenia
Uncommon: liver function tests abnormal
Immune system disorders
Uncommon: pruritus
Infections and infestations
Common: infection
Metabolism and nutrition disorders
Uncommon: peripheral oedema, hypercholesteremia
Musculoskeletal and connective tissue disorders
Uncommon: arthritis
Neoplasms benign, malignant and unspecified (incl cysts and polyps)
Uncommon: cystitis
Nervous system disorders
Common: headache
Uncommon: dizziness, somnolence, nervousness
Psychiatric disorders
Uncommon: insomnia, anxiety
Renal and urinary disorders
Uncommon: urine abnormality
Respiratory, thoracic and mediastinal disorders

Uncommon: rhinitis, bronchitis, cough increased, pharyngitis, sinusitis, dyspnoea
Skin and subcutaneous tissue disorders
Common: hirsutism
Uncommon: rash
Urogenital
Uncommon: cystitis, urine abnormality
Vascular disorders
Common: hypertension

8.5 Post-Market Adverse Reactions

The following adverse reactions have been identified during post-marketing use of LUMIGAN RC. 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: blepharal pigmentation, dry eye, eye discharge, eye edema, eyelid edema, eye pain, foreign body sensation in eyes, iris hyperpigmentation, lacrimation increased, 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, photophobia, macular edema, vision blurred

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

Nervous system disorders: headache

Respiratory, thoracic and mediastinal disorders: exacerbation of asthma

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

No specific drug interaction studies have been conducted. However, no drug-drug interactions are anticipated in humans since systemic drug concentrations of bimatoprost are extremely low (less than 0.2 ng/mL) following repeated ocular dosing with bimatoprost ophthalmic solution 0.03% and as metabolism and excretion involves multiple pathways.

9.4 Drug-Drug Interactions

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

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

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

10.2 Pharmacodynamics

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

In a short 5-day Phase 2 study, four formulations of bimatoprost were evaluated: 0.01%, 0.015%, 0.015%/EDTA, 0.02%, all preserved with 0.2 mg/mL benzalkonium chloride. LUMIGAN (bimatoprost) ophthalmic solution 0.03% (preserved 0.05 mg/mL benzalkonium chloride) served as the active control. Statistically and clinically significant decreases were observed in mean IOP change from baseline at each time point for all test formulations with lower bimatoprost concentrations (0.01%, 0.015%, 0.015% EDTA, and 0.02%) and higher benzalkonium chloride concentration (0.2 mg/mL), as well as for LUMIGAN.

10.3 Pharmacokinetics

Table 4 – Summary of Mean Bimatoprost Pharmacokinetic Parameters Following Once-daily Ocular Administration of Bimatoprost 0.03% to Each Eye of Healthy Subjects for 2 Weeks

Collection Day	C_{max} (ng/mL)	T_{max} (hr)	AUC (ng•hr/mL)[a]
1	0.0864	0.105	0.1024
7	0.0721	0.131	0.0742
14	0.0822	0.107	0.0960

[a] AUC refers to $AUC_{0\text{-}inf}$ on Day 1 and $AUC_{0\text{-}24h}$ on Days 7 and 14.

Systemic exposure after repeated ocular application is low. Steady state was achieved after one week

of once daily dosing with one drop of bimatoprost ophthalmic solution 0.03% to both eyes.

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

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

Absorption

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

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

The blood concentrations of bimatoprost from patients with open angle glaucoma or ocular hypertension in two Phase 3 safety and efficacy studies conducted with bimatoprost ophthalmic solution 0.03% were measured (N=88 on once-daily treatment and N=89 on twice-daily treatment). The samples were collected at approximately 5 minutes after the evening dose over a 3-month treatment period. Bimatoprost blood concentrations were similar to those observed in normal, healthy subjects and there was no significant systemic drug accumulation over time. The C-1 acid metabolite (AGN 191522) was typically not measurable in blood samples from these studies.

Therapeutic drug monitoring in the Phase 3 studies conducted with bimatoprost ophthalmic solution 0.03% showed that in one study that the elderly group had a higher concentration in the blood; however, this was not observed in the second Phase 3 study.

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

Distribution

Bimatoprost is moderately distributed into body tissues with a steady-state volume of distribution of 0.67 L/kg. In human blood, bimatoprost resides mainly in the plasma. Approximately 12% of bimatoprost remains unbound in human plasma. The in vitro binding of bimatoprost to synthetic melanin was ~20% at concentrations of 0.2 - 100 mcg/mL. The overall extent of melanin binding was not dependent on concentration, and the binding was reversible.

Metabolism

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

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

Elimination

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

Special Populations and Conditions

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

11 STORAGE, STABILITY AND DISPOSAL

LUMIGAN RC should be stored in the original container at 2-25°C. Discard unused solution at the end of treatment.

Keep out of reach and sight of children.

12 SPECIAL HANDLING INSTRUCTIONS

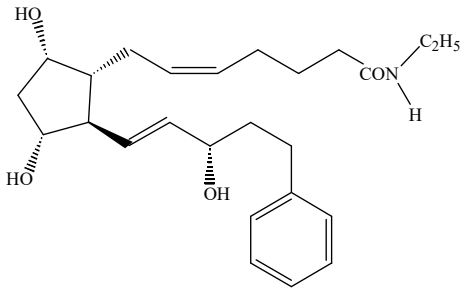
There are no special handling instructions.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Drug Substance

Proper name:	bimatoprost
Chemical name:	(Z)-7-[(1R,2R,3R,5S)-3,5-Dihydroxy-2-[1E,3S)-3-hydroxy-5-phenyl-1-pentenyl] cyclopentyl]-5-N-ethylheptenamide
Molecular formula and molecular mass:	$C_{25}H_{37}NO_4$; 415.58 g/mol
Structural formula:	
Physicochemical properties:	Bimatoprost is a white to off-white powder, which is very soluble in ethyl alcohol and methyl alcohol and slightly soluble in water

14 CLINICAL TRIALS

14.1 Clinical Trial by Indication

Reduction of Intraocular Pressure

Table 5 – Summary of patient demographics for clinical trial in the reduction of intraocular pressure

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
192024-031	Randomized, multicentre, double-blind, parallel	Bimatoprost 0.01% QD Bimatoprost 0.0125% QD Bimatoprost 0.03% QD (LUMIGAN) Ophthalmic; one drop into each affected eye per regimen above 12 months	Bimatoprost 0.01%: 186 Bimatoprost 0.0125%: 188 Bimatoprost 0.03%: 187	63.5 years (23 - 94)	M: 240 F: 321

A 12-month clinical study was conducted in patients with open angle glaucoma or ocular hypertension with a baseline IOP of ≥ 22 and ≤ 34 mm Hg, and with no severe dry eye. The results of comparing LUMIGAN RC (bimatoprost) to LUMIGAN are presented.

The primary efficacy endpoint was mean IOP at all time points, assessed using an equivalence analysis. Equivalence of efficacy was achieved if the upper and lower limits of the two sided 95% and 97.5% confidence intervals (CI) for the between treatment difference in IOP were within ±1.50 mm Hg at all post baseline timepoints and were within ±1.00 mm Hg at a majority of the post baseline timepoints. The between treatment difference was calculated as LUMIGAN RC minus LUMIGAN; thus, a larger (positive) difference favoured LUMIGAN. A confidence interval approach and Hochberg's method was employed to adjust the significance level for between group comparisons.

Results of study 192024-031 in reduction of intraocular pressure:

Approximately 90% of the enrolled patients completed the 12-month study, that is, 171 (91.9%) in the LUMIGAN RC group, and 162 (86.6%) in the LUMIGAN group.

Results for mean IOP show that LUMIGAN RC met the definition of equivalence to LUMIGAN (i.e., the difference in mean IOP between treatment groups was within ±1.50 mm Hg at all post baseline (17/17) timepoints, and within ±1.00 mm Hg at the majority of post baseline timepoints (9/17), based on 95% CIs). LUMIGAN RC was also equivalent to LUMIGAN for the secondary efficacy endpoint, mean diurnal IOP: the 95% CIs of the between treatment difference were within ±1.50 mm Hg for 6/6 post baseline visits, and at 4/6 visits were within ±1.00 mm Hg. However, responders' rates defined as patients (%)

achieving a target pressure of < 18 mm Hg at every timepoint was numerically larger with LUMIGAN (24.6%) than with LUMIGAN RC (17.2%), p-value = 0.07.

Table 6 –Mean Intraocular Pressure (mm Hg), and mean change from baseline for LUMIGAN RC and LUMIGAN

		Mean IOP	Mean IOP change from baseline
Visit	**Timepoint**	**LUMIGAN RC / LUMIGAN N = 186 / 187**	**LUMIGAN RC / LUMIGAN N = 186 / 187**
Baseline	Hour 0	25.1 / 25.0	-
	Hour 4	23.0 / 23.2	-
	Hour 8	22.3 / 22.3	-
	Hour 0	17.8 / 17.3	-7.3 / -7.7
	Difference[a]	**0.56**	**0.42**
	(95% CI[b])	(-0.10 to 1.22)	
Week 2	Hour 4	17.1 / 16.3	-5.9 / -7.0
	Difference	**0.84**	**1.07**
	(95% CI)	(0.21 to 1.46)	
	Hour 8	16.9 / 16.2	-5.4 / -6.1
	Difference	**0.73**	**0.68**
	(95% CI)	(0.10 to 1.35)	
	Hour 0	17.6 / 17.2	-7.5 / -7.7
	Difference	**0.37**	**0.24**
	(95% CI)	(-0.25 to 1.00)	
Week 6	Hour 4	16.8 / 16.5	-6.2 / -6.8
	Difference	**0.29**	**0.52**
	(95% CI)	(-0.31 to 0.89)	
	Hour 8	16.7 / 16.4	-5.6 / -5.8
	Difference	**0.23**	**0.19**
	(95% CI)	(-0.37 to 0.82)	
	Hour 0	17.3 / 17.0	-7.8 / -8.0
	Difference	**0.33**	**0.19**
	(95% CI)	(-0.31 to 0.97)	
Month 3	Hour 4	16.7 / 16.1	-6.3 / -7.1
	Difference	**0.55**	**0.78**
	(95% CI)	(-0.05 to 1.16)	(0.09 to 1.48)
	Hour 8	16.4 / 16.2	-5.9 / -6.1
	Difference	**0.28**	**0.24**
	(95% CI)	(-0.31 to 0.87)	
	Hour 0	17.7 / 17.4	-7.4 / -7.6
	Difference	**0.39**	**0.25**
	(95% CI)	(-0.25 to 1.03)	

		Mean IOP	Mean IOP change from baseline
Visit	**Timepoint**	**LUMIGAN RC / LUMIGAN N = 186 / 187**	**LUMIGAN RC / LUMIGAN N = 186 / 187**
Month 6	Hour 4	17.0 / 16.3	-6.0 / -6.9
	Difference	**0.63**	**0.86**
	(95% CI)	(0.01 to 1.25)	
	Hour 8	16.6 / 16.3	-5.7 / -6.0
	Difference	**0.35**	**0.31**
	(95% CI)	(-0.23 to 0.94)	
	Hour 0	17.9 / 17.8	-7.2 / -7.2
	Difference	**0.13**	**-0.01**
	(95% CI)	(-0.52 to 0.78)	
Month 9	Hour 4	17.1 / 16.9	-5.9 / -6.3
	Difference	**0.22**	**0.45**
	(95% CI)	(-0.41 to 0.85)	
	Hour 0	17.7 / 17.3	-7.4 / -7.6
	Difference	**0.41**	**0.27**
	(95% CI)	(-0.26 to 1.07)	
Month 12	Hour 4	17.2 /16.9	-5.8 / -6.3
	Difference	**0.29**	**0.52**
	(95% CI)	(-0.37 to 0.96)	
	Hour 8	17.1 / 16.7	-5.2 / -5.6
	Difference	**0.44**	**0.40**
	(95% CI)	(-0.18 to 1.06)	

a Difference is calculated as test formulation minus LUMIGAN; a positive value favoured LUMIGAN over LUMIGAN RC.
b 95% for between-treatment difference based on one-way ANOVA model for fixed effect of treatment

Over the 12 months of Study 192024-031, the efficacy of LUMIGAN RC was maintained (Table 7). Mean IOP and mean changes from baseline IOP, at peak and trough, were significantly decreased with LUMIGAN RC, showing a sustained therapeutic effect.

Table 7 – Mean IOP and Mean Change from Baseline IOP (mm Hg) at Each Timepoint for LUMIGAN RC in Study 192024-031

	LUMIGAN RC (N=186)						
	Baseline	**Week 2**	**Week 6**	**Month 3**	**Month 6**	**Month 9**	**Month 12**
Mean Intraocular Pressure (mm Hg)							
Hour 0	25.1	17.8	17.6	17.3	17.7	17.9	17.7
Hour 4	23.0	17.1	16.8	16.7	17.0	17.1	17.2
Hour 8	22.3	16.9	16.7	16.4	16.6	NA	17.1
Mean Change from Baseline Intraocular Pressure (mm Hg)							
Hour 0	25.1	-7.3*	-7.5*	-7.8*	-7.4*	-7.2*	-7.4*
Hour 4	23.0	-5.9*	-6.2*	-6.3*	-6.0*	-5.9*	-5.8*
Hour 8	22.3	-5.4*	-5.6*	-5.9*	-5.7*	NA	-5.2*

Source: Report 192024-031, Tables 14.2-1.1 to 14.2-1.7 and 14.2-2.1 to 14.2-2.7
* statistically significant change from baseline ($p < 0.001$); NA = Not applicable

Compared to LUMIGAN, LUMIGAN RC had significantly fewer adverse events (all causality and treatment-related), and significantly fewer ocular adverse events. Patients experienced less severe macroscopic hyperaemia.

Only few patients discontinued due to treatment-related adverse events: 2.2% (4/185) for LUMIGAN RC, compared to 6.4% (12/187) for LUMIGAN. Discontinuation over time due to ocular adverse events was significantly different between LUMIGAN RC and LUMIGAN.

Evaluations of LUMIGAN RC beyond 12 months have not been conducted.

However, extensions study of the two 12-month trials (008 and 009) using LUMIGAN was conducted. The long-term safety data of LUMIGAN with regards to iris pigmentation was primarily assessed. Please refer to the Product Monograph of LUMIGAN for detailed information.

Increased iris pigmentation was reported in 16/957 (1.7%) of patients receiving any dose of LUMIGAN (i.e., QID or BID) and occurred during the first year of treatment. There were no additional reports or increases in severity after the first year in 3/16 patients with increased pigmentation who continued treatment for an additional 3 years of dosing (4 years total treatment). However, this may be due in part to the small number of patients followed up or to the low sensitivity/expected variability of the photographic methods assessing pigmentation, or both.

No patients discontinued treatment with LUMIGAN due to increased iris pigmentation.

Twenty-seven patients who completed the 4-year extension study were enrolled in an open label follow-up for an additional year of treatment with LUMIGAN: 20 of these 27 patients were previously treated with LUMIGAN for 4 years. One patient experienced an increase in iris pigmentation during the first year of treatment with LUMIGAN, but no intensification of pigmentation was noted in this patient in the 5th year extension as compared to the baseline photography.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

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

In an in vitro cytotoxicity assay (TX04059/PK-04-168), dose-dependant cytotoxicity related to benzalkonium chloride was noted in rabbit corneal epithelial cell layers (RCECL). The cytotoxicity seen with bimatoprost 0.015%, benzalkonium chloride 0.2 mg/mL was 1.7 to 2 times more intense than with LUMIGAN (benzalkonium chloride 0.05 mg/mL, 0.03%). Note that several factors are believed to decrease the clinical significance of the in vitro findings. These are, (1) a rapid dilution of a topically applied solution containing benzalkonium chloride due to normal tear film dynamics, and (2) the properties of the in vivo eye such as tear flow, tear proteins, a mucin coating, and a multi-layer structure with rapid epithelial regeneration.

Long-term Toxicity: No treatment-related ocular or systemic effects were produced in Dutch belted rabbits when 0.03% or 0.1% bimatoprost ophthalmic formulation was instilled to the eye once or twice daily for 6 months. The highest dose (0.1% twice daily) produced 53 times the systemic drug exposure seen in humans treated with 1 drop in each eye of bimatoprost ophthalmic solution 0.03% once daily for 2 weeks. No treatment-related systemic effects were observed in cynomolgus monkeys when 0.03% or 0.1% bimatoprost ophthalmic formulation was instilled to the eye once or twice daily for 1 year. An increase in iris pigmentation was noted in some animals in all treated groups. No associated increase in melanocyte number was observed with the pigmentation. It appears that the mechanism of increased iris pigmentation is due to increased stimulation of melanin production in melanocytes and not to an increase in melanocyte number. Reversible dose-related periocular effects characterized by a prominent upper and/or lower sulcus and widening of the palpebral fissure of the treated eye was also observed. No functional or microscopic change related to the periocular change was observed. The highest dose (0.1% twice daily) produced at least 65 times the systemic drug exposure seen in humans treated with 1 drop into each eye of bimatoprost ophthalmic solution 0.03% once daily for 2 weeks. (Human dose calculated as 21 mcg in a 35 mcL drop dosed once daily in both eyes - not based on the 28 mcL drop size as used in the Phase III studies.)

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

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

No effects were observed in mice given 4 mg/kg/day bimatoprost orally for 3 months. This dose

achieved systemic exposure that was 149 times higher than that observed in humans treated with bimatoprost ophthalmic solution 0.03% with 0.05 mg/mL benzalkonium chloride, one drop/day in both eyes for 14 days. Female mice given oral doses of 8 mg/kg/day showed a reversible thymic lymphoid proliferation. This effect was observed only in mice and at a dose 460-fold higher than that observed in humans given bimatoprost ophthalmic solution 0.03% with 0.05 mg/mL benzalkonium chloride, one drop/day in both eyes for 14 days.

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

A slight, reversible increase in alanine aminotransferase and aspartate aminotransferase was observed in rats given ≥ 0.1 mg/kg/day orally for 1 year. There were no associated microscopic liver findings. A dose-related, reversible cellular vacuolation of corpora lutea at ≥ 0.3 mg/kg/day in female rats was observed. The lowest effect dose of 0.1 mg/kg/day achieved systemic exposure (C_{max}) that was 8 times higher than that observed in humans treated with bimatoprost ophthalmic solution 0.03% with 0.05 mg/mL benzalkonium chloride, one drop/day in both eyes for 14 days. Hepatic and ovarian effects in rats were considered species-specific since these changes have not been observed in mice and monkeys at systemic exposures up to 2,800- to 14,000-fold higher, respectively, than those in humans given bimatoprost ophthalmic solution 0.03% with 0.05 mg/mL benzalkonium chloride, one drop/day in both eyes for 14 days.

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

Carcinogenicity: Bimatoprost was not carcinogenic when administered once daily orally (by gavage) at doses of 0.3, 1.0 and 2.0 mg/kg/day to mice and 0.1, 0.3 and 1.0 mg/kg/day to rats (192 or 291 times the human exposure based on blood AUC levels from subjects given bimatoprost ophthalmic solution 0.03% with 0.05 mg/mL benzalkonium chloride, one drop/day in both eyes for 14 days) for 104 weeks.

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

Salmonella/Escherichia Coli Mutagenicity Assay:

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

Mouse Lymphoma Mutagenesis Assay:

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

In vivo Mouse Micronucleus Assay:

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

Reproductive and Developmental Toxicology:

Impairment of Fertility:

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

Pregnancy/Teratogenic Effects:

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

Perinatal and Postnatal:

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

Animal Lactation:

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

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

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr]LUMIGAN RC®

bimatoprost ophthalmic solution

Read this carefully before you start using **LUMIGAN RC** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **LUMIGAN RC**.

What is LUMIGAN RC used for?

LUMIGAN RC eye drops are used to reduce high pressure in the eye in adult patients with open-angle glaucoma or ocular hypertension. If the high pressure is not reduced, it could eventually damage your sight.

How does LUMIGAN RC work?

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

What are the ingredients in LUMIGAN RC?

Medicinal ingredient: bimatoprost

Non-medicinal ingredients: benzalkonium chloride, as preservative; citric acid monohydrate, purified water, sodium chloride, and sodium phosphate dibasic heptahydrate. Sodium hydroxide and/or hydrochloric acid may be added to adjust pH.

LUMIGAN RC comes in the following dosage forms:

Ophthalmic solution, 0.01% w/v

Do not use LUMIGAN RC if:

- you are allergic to bimatoprost, to any of the other ingredients, or to any of the parts of the container (see section **What are the ingredients in Lumigan RC?**).

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

- are taking, or have recently taken, any other medicines. Using LUMIGAN RC with other medicines or other antiglaucoma products may reduce their effectiveness.

- are pregnant or planning to become pregnant. You should ask your healthcare professional for advice before taking any medicine.
- are breastfeeding or plan to breastfeed. Ask your healthcare professional how to feed your baby while using LUMIGAN RC.
- have an active eye infection, inflammation (e.g. uveitis) or any other eye or eyelid condition.
- develop another eye condition (an injury or an infection).
- have severe dry eyes.
- need to have eye surgery.
- have liver or kidney problems.

Other warnings you should know about:

Changes in eye and eyelid color:

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

Hair growth:

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

Changes in vision:

Using LUMIGAN RC may temporarily blur your vision. Do not drive or use machines until your vision has cleared.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with LUMIGAN RC:

No drug interaction studies have been done with LUMIGAN RC.

How to use LUMIGAN RC:

- Do not use the bottle if the tamper-proof seal on the bottle neck is broken before you first use it.
- Always use LUMIGAN RC exactly as your healthcare professional has instructed you.
- LUMIGAN RC contains a preservative called benzalkonium chloride which may discolor soft contact lenses. If you wear contact lenses, remove them before using LUMIGAN RC. Wait 15 minutes after using the drops before you put your lenses back in.

- If you use LUMIGAN RC with another eye drop, wait at least five minutes after using LUMIGAN RC before using the other drops.
- To help prevent infections, do not let the tip of the bottle touch your eye or anything else. Put the cap back on and close the bottle immediately after you have used it.

Follow these steps to use LUMIGAN RC properly:

- Wash your hands. Tilt your head back and look at the ceiling. (See Illustration 1)
- Gently pull down the lower eyelid to create a small pocket. (See Illustration 2)
- Turn the bottle upside down and squeeze it gently to release one drop into the eyelid pocket. If a drop misses your eye, try again. (See Illustration 3)
- Let go of the lower lid, and close your eye for 30 seconds. (See Illustration 4)

- Repeat steps 1 – 4 in the other eye if both eyes need treatment.

Usual dose:

Adults: One drop of LUMIGAN RC in each eye that needs treatment, once every day, in the evening.

Overdose:

If you accidentally use too many drops, just go back to your regular once a day dosing the next day.

If you think you, or a person you are caring for, have used too much LUMIGAN RC, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

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

What are possible side effects from using LUMIGAN RC?

These are not all the possible side effects you may have when using LUMIGAN RC. If you experience any side effects not listed here, tell your healthcare professional.

Like all medicines, LUMIGAN RC can have side effects. Most of the side effects are not serious. If these persist or cause you concern, consult your healthcare professional.

Side effects may include:

- Darkening of the eyelid
- Eye irritation, redness, itching
- Excessive hair growth
- Longer eyelashes, change in eyelash color
- Red and/or itchy eyelids
- Small breaks in the surface of the eye
- Deepening and drooping of the eyelid

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

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

LUMIGAN RC should be stored in the original container at 2 to 25°C. Discard unused solution at the end of treatment.

Do not use the drops after the expiry date (marked “Exp”) on the bottle and the box.

Keep out of reach and sight of children.

If you want more information about LUMIGAN RC:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the

manufacturer's website www.abbvie.ca, or by calling 1-888-704-8271.

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