PRODUCT MONOGRAPH

[Pr]LUMIGAN RC®

Bimatoprost

Ophthalmic Solution 0.01% w/v

Elevated Intraocular Pressure Therapy

Prostamide Analogue

Allergan Inc.
Markham, ON
L6G 0B5

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Ophthalmic Solution 0.01% w/v

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Ophthalmic	Solution, 0.01% w/v bimatoprost	Benzalkonium chloride 0.2 mg/mL as preservative *For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

LUMIGAN RC® (bimatoprost ophthalmic solution 0.01% w/v) is indicated for:

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

Geriatrics (> 65 years of age):
No overall clinical differences in safety or effectiveness have been observed between elderly and other adult patients. Use as for adult patients.

Pediatrics (<18 years of age):
Not recommended for pediatric use. Safety and effectiveness in pediatric patients have not been established.

CONTRAINDICATIONS

- Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see the Dosage Forms, Composition and Packaging section of the product monograph.

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 colour 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® (bimatoprost ophthalmic solution 0.01% w/v) 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 Part III Consumer Information.

Carcinogenesis and Mutagenesis
See Toxicology.

Hepatic/Biliary/Pancreatic
LUMIGAN RC® has not been studied in patients with hepatic impairment and should therefore be used with caution in such patients.

Occupational Hazards
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.

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 intraocular pressure (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 prostanglandin 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.

Sexual Function/Reproduction

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).

Special Populations

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

Maternal toxicity, evidenced by reduced gestation length, late resorptions, fetal death, postnatal mortality and reduced pup body weights were observed when female rats received oral doses which were at least 41 times the intended 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). Cohabitation times in the offspring were increased but neurobehavioural functions were not affected.

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.

Nursing Women: 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.

ADVERSE REACTIONS

Adverse Drug 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).

Clinical Trial Adverse Drug Reactions

> *Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.*

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 1, using MedDRA System Organ Class, for LUMIGAN RC® and LUMIGAN®.

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

SOC[a] Preferred Term	**LUMIGAN RC® N = 185**	**LUMIGAN® N = 187**
All Ocular Events	88 (47.6%)[b]	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%)

SOC[a] **Preferred Term**	**LUMIGAN RC®** **N = 185**	**LUMIGAN®** **N = 187**
All Ocular Events	88 (47.6%)[b]	116(62.0%)
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%)
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 & administration site conditions		
instillation site irritation*	2 (1.1%)	1 (0.5%)
Infections &infestations		
hordeolum	1 (0.5%)	2 (1.1%)

Investigations		
intraocular pressure increased	0 (0.0%)	3 (1.6%)
Skin & subcutaneous tissue disorders		
skin hyperpigmentation*	5 (2.7%)	10 (5.3%)
hypertrichosis* [c]	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 Coding based on MedDRA

b LUMIGAN RC® significantly less than LUMIGAN® ($p \leq 0.005$)

c 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 2: Number (%) of Patients with Non-ocular Adverse Events, Regardless of Causality, Reported by > 1% of Patients treated with LUMIGAN RC® (Study 192024-031)

SOC[a] Preferred Term	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%)
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%)

[a] Coding based on MedDRA

* Event reported by an investigator as treatment-related for at least one patient for LUMIGAN RC®.

Less Common Clinical Trial Adverse Events (<1%) Reported in Clinical Trials with LUMIGAN RC®

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 discolouration, 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

Post-Market Adverse Drug Reactions
The following adverse reactions have been identified during postmarketing use of LUMIGAN RC®. 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: blepharal pigmentation, dry eye, eye discharge, eye edema, eyelid edema, eye pain, foreign body sensation in eyes, iris hyperpigmentation, lacrimation increased, periorbital and lid changes including deepening of the eyelid sulcus, 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

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.

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.

Drug-Food Interactions
Interactions with food have not been established.

Drug-Herb Interactions
Interactions with herbal products have not been established.

Drug-Laboratory Interactions
Interactions with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

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® (bimatoprost ophthalmic solution 0.01% w/v) should not exceed once daily since it has been shown that more frequent administration of bimatoprost ophthalmic solution may lessen the IOP lowering effect, and increase the frequency and severity of adverse events. (see WARNINGS and PRECAUTIONS, Ophthalmologic).

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

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 WARNINGS and PRECAUTIONS, Ophthalmologic).

OVERDOSAGE

For management of a suspected drug overdose, including accidental ingestion, contact your regional Poison Control Centre.

No information is available on overdosage in humans. If overdose with LUMIGAN RC® (bimatoprost ophthalmic solution 0.01% w/v) 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 10 kg child would be exposed were it to accidentally ingest the contents of one 7.5 mL bottle of LUMIGAN RC®.

ACTION AND CLINICAL PHARMACOLOGY

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.

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.

Pharmacokinetics

After one drop of bimatoprost ophthalmic solution 0.03% was administered once daily to both eyes of 15 healthy subjects, blood bimatoprost 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.

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, with mean Cmax values of 0.07 and 0.08ng/mL on day 7 and 14, respectively, and mean AUC 0-24h of 0.074 and 0.096 ng•hr/mL on day 7 and 14, respectively.

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 μL 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 is rapidly absorbed across the human cornea and sclera, with scleral penetration being more efficient. Animal studies show that it is well distributed into ocular tissues following ocular administration, where only minimal metabolism occurs in humans.

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. 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.

Excretion: Following an intravenous dose of radiolabelled 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. 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.

STORAGE AND STABILITY

LUMIGAN RC® (bimatoprost ophthalmic solution 0.01% w/v) should be stored in the original container at 2º-25ºC. Discard unused solution at the end of treatment.
Keep in a safe place out of the reach of children.

DOSAGE FORMS, COMPOSITION AND PACKAGING

LUMIGAN RC® (bimatoprost ophthalmic solution 0.01% w/v) is supplied sterile in white opaque plastic ophthalmic dispenser bottles in the following sizes: 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.

Each mL of LUMIGAN RC® contains bimatoprost 0.1 mg with the following non-medicinal ingredients: benzalkonium chloride 0.2 mg as preservative, sodium chloride, sodium phosphate dibasic heptahydrate, citric acid monohydrate, and purified water. Sodium hydroxide and/or hydrochloric acid may be added to adjust pH.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

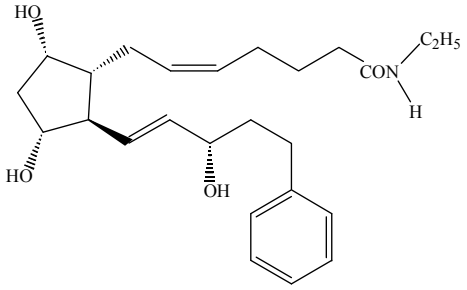
Drug Substance

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

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.

CLINICAL TRIALS

Study demographics and trial design

Table 3: Summary of patient demographics for study 192024-031

Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range)	Gender
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 mmHg, and with no severe dry eye. The results of comparing LUMIGAN RC® (bimatoprost ophthalmic solution 0.01% w/v) 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.

Study results

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 4: 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)	

		Mean IOP	Mean IOP change from baseline
Visit	**timepoint**	**LUMIGAN RC® / LUMIGAN® N = 186 / 187**	**LUMIGAN RC® / LUMIGAN® N = 186 / 187**
Week 2	Hour 4 Difference (95% CI)	17.1 / 16.3 **0.84** (0.21 to 1.46)	-5.9 / -7.0 **1.07**
	Hour 8 Difference (95% CI)	16.9 / 16.2 **0.73** (0.10 to 1.35)	-5.4 / -6.1 **0.68**
Week 6	Hour 0 Difference (95% CI)	17.6 / 17.2 **0.37** (-0.25 to 1.00)	-7.5 / -7.7 **0.24**
	Hour 4 Difference (95% CI)	16.8 / 16.5 **0.29** (-0.31 to 0.89)	-6.2 / -6.8 **0.52**
	Hour 8 Difference (95% CI)	16.7 / 16.4 **0.23** (-0.37 to 0.82)	-5.6 / -5.8 **0.19**
Month 3	Hour 0 Difference (95% CI)	17.3 / 17.0 **0.33** (-0.31 to 0.97)	-7.8 / -8.0 **0.19**
	Hour 4 Difference (95% CI)	16.7 / 16.1 **0.55** (-0.05 to 1.16)	-6.3 / -7.1 **0.78** (0.09 to 1.48)
	Hour 8 Difference (95% CI)	16.4 / 16.2 **0.28** (-0.31 to 0.87)	-5.9 / -6.1 **0.24**
Month 6	Hour 0 Difference (95% CI)	17.7 / 17.4 **0.39** (-0.25 to 1.03)	-7.4 / -7.6 **0.25**
	Hour 4 Difference (95% CI)	17.0 / 16.3 **0.63** (0.01 to 1.25)	-6.0 / -6.9 **0.86**
	Hour 8 Difference (95% CI)	16.6 / 16.3 **0.35** (-0.23 to 0.94)	-5.7 / -6.0 **0.31**
Month 9	Hour 0 Difference (95% CI)	17.9 / 17.8 **0.13** (-0.52 to 0.78)	-7.2 / -7.2 **-0.01**
	Hour 4 Difference (95% CI)	17.1 / 16.9 **0.22** (-0.41 to 0.85)	-5.9 / -6.3 **0.45**

		Mean IOP	Mean IOP change from baseline
Visit	**timepoint**	**LUMIGAN RC® / LUMIGAN® N = 186 / 187**	**LUMIGAN RC® / LUMIGAN® N = 186 / 187**
Month 12	Hour 0 Difference (95% CI)	17.7 / 17.3 **0.41** (-0.26 to 1.07)	-7.4 / -7.6 **0.27**
	Hour 4 Difference (95% CI)	17.2 /16.9 0.29 (-0.37 to 0.96)	-5.8 / -6.3 **0.52**
	Hour 8 Difference (95% CI)	17.1 / 16.7 **0.44** (-0.18 to 1.06)	-5.2 / -5.6 **0.40**

[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 5). Mean IOP and mean changes from baseline IOP, at peak and trough, were significantly decreased with LUMIGAN RC®, showing a sustained therapeutic effect.

Table 5: 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.

DETAILED PHARMACOLOGY

Animal Pharmacology

Ocular Studies

Studies in ocular normotensive and laser-induced ocular hypertensive cynomolgus monkeys indicated that bimatoprost potently reduces intraocular pressure. Five-day studies in ocular normotensive monkeys and one day studies in ocular hypotensive monkeys demonstrated that a 0.001% dose of bimatoprost could significantly lower intraocular pressure. Five day studies in ocular normotensive Beagle dogs confirmed bimatoprost as a potent ocular hypotensive over a dose range of 0.001% to 0.1% when given either once daily or twice daily.

Bimatoprost did not alter pupil diameter in monkeys at the 0.1% dose. This is in contrast to

Beagle dog studies, where 0.001% to 0.1% doses produced miosis.

Morphologic changes in the anterior eye segment of cynomolgus monkeys unilaterally topically treated for one year with either latanoprost 0.005%, bimatoprost 0.03%, or two prostaglandin EP agonists were investigated. The general morphology of the ciliary muscle and trabecular meshwork was normal in appearance and shape in all animals, whereas similar localized morphologic changes were observed in all four treatment groups. The enlargement of uveoscleral outflow routes and morphologic changes in the trabecular meshwork may be suggestive of increased uveoscleral and conventional outflow. In the affected ciliary muscle areas, sprouting of nerve fibers may be the consequence of tissue remodeling.

Cardiovascular Effects

Bimatoprost given by single intravenous injection at up to 10 µg/kg to dogs, by intravenous injection at up to 1 mg/kg/day for 17 weeks to monkeys, or by topical ocular instillation at up to 0.1%/drop/day for 52 weeks to monkeys did not cause cardiovascular effects. In particular, there was no change in the QTc interval.

Metabolism and Pharmacokinetics

Ocular Pharmacokinetics

Following a single ocular instillation of ^{3}H-bimatoprost to rabbits and single and multiple ocular instillations to monkeys, bimatoprost was absorbed rapidly and was well distributed in the eye. The absorbed radioactivity was found mainly in the anterior segment of the eye and the highest concentrations of radioactivity were found in the conjunctiva, cornea, sclera, iris, and ciliary body in both rabbit and monkey eyes. Maximal concentrations in these tissues were reached within 0.5 to 2 hours post-dose. Twenty-four hours after the last dose in monkeys, bimatoprost concentrations in the ciliary body (the purported site of action) were still over 5-fold higher than the *in vitro* EC_{50} value of 14 ng/mL required for pharmacological effect.

Following a single ocular instillation of LUMIGAN® or 0.03% bimatoprost/ 0.2 mg/mL ppm benzalkonium chloride formulation to rabbits, bimatoprost was absorbed into the eye and extensively metabolized to AGN-191522 (study PK-04-102). Due to the extensive metabolism of bimatoprost in rabbit eyes, AGN-191522 was used as a surrogate for determining ocular absorption of AGN-192024. Increasing benzalkonium chloride concentration from 0.05 to 0.2 mg/mL resulted in 57% higher aqueous humor drug concentration.

In an *in vitro* permeability assay using a rabbit corneal epithelial cell layers (RCECL) model, 0.015% bimatoprost formulations containing benzalkonium chloride (0, 50, 125, 150, 200 ppm) dose dependently increased bimatoprost permeability (study PK-04-168). Although there is a dose dependent cytotoxicity in this *in vitro* assay (see table below), the cell viability after 2 hr exposure to 0.015% bimatoprost formulation containing 0.2 mg/mL benzalkonium chloride was 81-82% compared to a cell viability of 89-91% after 2 hr exposure to LUMIGAN®.

Table 6: The effect of benzalkonium chloride on bimatoprost permeability (Papp) and cell

viability in RCECL model (study PK-04-168/TX04059)

BAK Concentration (mg/mL)	Papp (x 10^{-6} cm/sec)_	Cell Viability (%)
0	0.161	97-98
50	0.377	86-93
125	0.865	83-86
150	0.984	83-84
200	1.42	81-82

Following twice daily topical applications (30 µL each) of one of four reformulations of LUMIGAN® ophthalmic solutions or vehicle ophthalmic solution in the left eye for 1 month in female NZW rabbits (9 rabbits/formulation), the following conclusions were made:

Blood AGN 191522 (the metabolite of bimatoprost) concentrations were below the lower limit of quantitation in all samples;

Systemic exposures of bimatoprost were similar among the four active treatment groups on both Days 7 and 28 despite differences in dosage strength (i.e. 0.03% vs 0.015% vs 0.02%); the new formulations produced similar systemic bimatoprost concentrations despite differences in dosage strength (**PK-05-070**).

Table 7: The blood toxicokinetic parameters for bimatoprost (study PK-05-070)

Sample Time-point	**Treatment**	**Cmax** (ng/mL)	**Tmax** (hours)	**AUC** (ng*hr/mL)	**AUC Interval (hr)**
Day 7	LUMIGAN® (Bimatoprost 0.03% w/ 0.05 mg/mL benzalkonium chloride)	0.571±0.071	0.167	0.179±0.009	0-0.50
	Bimatoprost 0.015% w/ 0.2 mg/mL BAK	0.737±0.617	0.083	0.132±0.028	0-0.33
	Bimatoprost 0.020% w/ 0.2 mg/mL BAK	0.523±0.107	0.083	0.139±0.008	0-0.50
	Bimatoprost 0.015% w/ 0.2 mg/mL BAK & 0.03% EDTA	0.326±0.138	0.083	0.049±0.006	0-0.25
Day 28	LUMIGAN® (Bimatoprost 0.03% w/ 0.05 mg/mL BAK)	0.649±0.181	0.083	0.208±0.012	0-0.50
	Bimatoprost 0.015% w/ 0.2 mg/mL BAK	0.539±0.134	0.083	0.094±0.008	0-0.33
	Bimatoprost 0.020% w/ 0.2 mg/mL BAK	0.901±0.293	0.083	0.191±0.013	0-0.50
	Bimatoprost 0.015% w/ 0.2 mg/mL BAK & 0.03% EDTA	0.451±0.135	0.083	0.095±0.009	0-0.33

AGN 192024 = bimatoprost ; AGN 191522 = metabolite; BAK = benzalkonium chloride.
N = 9 rabbits/formulation

In a 6-month study, the left eye of male and female Dutch-Belted (DB) rabbits (N = 6/sex/group) received one drop daily of bimatoprost ophthalmic solution containing benzalkonium chloride 0.2 mg/mL with bimatoprost 0.01%, 0.0125 or 0% (placebo) either one drop per day (Groups 2 and 4) or one drop three times (Groups 1, 3, and 5) daily for 180 days. Blood samples were collected (N = 3/sex/group/timepoint) at predose, 5, 10, 20, 30, and 40 minutes after the last dose administration (after the 1st dose administration for Groups 2 and 4 and after the 3rd dose administration for Groups 1, 3, and 5). Blood samples were collected at these timepoints on Day 7 and at 1 month (Day 29), 3 months (Day 85) and 6 months (Day 180) for toxicokinetic evaluation. Blood bimatoprost and AGN 191522 concentrations were determined with a quantitation range of 0.125-100 ng/mL for bimatoprost and 0.250-100 ng/mL for AGN 191522.

The overall mean blood toxicokinetic parameters of bimatoprost and AGN 191522 are summarized in the following table:

Table 8: Overall Mean Blood Toxicokinetic Parameters of bimatoprost and AGN 191522

	Study Day	Treatment Group*	C_{max} (ng/mL)		T_{max} (min)	AUC_{0-t} (ng•min/mL)		AUC Interva (min)
			Mean	SD		Mean	SE	
AGN 192024	7	2	BLQ	NC	NC	NC	NC	NC
		3	BLQ	NC	NC	NC	NC	NC
		4	0.135	0.110	5	0.338	0.112	0-5
		5	0.198	0.116	5	0.495	0.118	0-5
	29 (1 mo.)	2	0.098	0.077	5	0.245	0.078	0-5
		3	0.276	0.110	5	0.690	0.112	0-5
		4	0.222	0.123	5	1.61	0.31	0-10
		5	0.364	0.092	5	2.37	0.24	0-10
	85 (3 mos.)	2	0.366	0.227	5	0.915	0.232	0-5
		3	0.211	0.147	5	0.528	0.150	0-5
		4	0.317	0.145	5	1.84	0.31	0-10
		5	0.276	0.152	5	1.58	0.32	0-10
	180 (6 mos.)	2	0.333	0.152	5	1.87	0.32	0-10
		3	0.178	0.092	5	0.445	0.094	0-5
		4	0.289	0.249	5	0.723	0.254	0-5
		5	0.372	0.167	5	2.31	0.36	0-10
AGN 191522	7	2	BLQ	NC	NC	NC	NC	NC
		3	BLQ	NC	NC	NC	NC	NC
		4	0.219	0.242	5	0.548	0.247	0-5
		5	0.275	0.227	5	0.688	0.232	0-5
	29 (1 mo.)	2	BLQ	NC	NC	NC	NC	NC
		3	BLQ	NC	NC	NC	NC	NC
		4	BLQ	NC	NC	NC	NC	NC
		5	BLQ	NC	NC	NC	NC	NC
	85 (3 mos.)	2	BLQ	NC	NC	NC	NC	NC
		3	BLQ	NC	NC	NC	NC	NC
		4	BLQ	NC	NC	NC	NC	NC
		5	0.178	0.199	5	0.445	0.203	0-5
	180 (6 mos.)	2	BLQ	NC	NC	NC	NC	NC
		3	BLQ	NC	NC	NC	NC	NC
		4	BLQ	NC	NC	NC	NC	NC
		5	BLQ	NC	NC	NC	NC	NC

Treatment 1: Placebo Control, 1 drop OS 3x daily
Treatment 2: 0.01% bim , 1 drop OS 1x daily
Treatment 3: 0.01% bim , 1 drop OS 3x daily
*N = 3/sex/group/timepoint (for all groups)
Treatment 4: 0.0125% bim , 1 drop OS 1x daily
Treatment 5: 0.0125% bim , 1 drop OS 3x daily

AGN 192024 = bimatoprost ; AGN 191522 = metabolite;

All solutions contained benzalkonium chloride 0.2 mg/mL

Systemic Absorption Following Ocular and Oral Administration

Bimatoprost was systemically absorbed after ophthalmic administration to rabbits and monkeys. The C_{max} in plasma was 3.23 ng-eq/mL in monkeys following twice-daily ocular administration of 0.1% bimatoprost for 10 days and 6.28 ng-eq/mL in rabbits following a single administration of 0.1%. The oral bioavailability of bimatoprost was 40%, 29% and 3% in mice, rats and monkeys, respectively. The low oral bioavailability in monkeys was attributed to extensive first-pass metabolism.

Systemic Disposition after Intravenous Administration

Following intravenous administration to mice, rats and monkeys bimatoprost had a moderate apparent volume of distribution at steady state ranging from 2.1 to 6.0 L/kg. Bimatoprost had a mean residence time of 0.28 hr in mice, 0.42 hr in rats and 0.93 hr in monkeys, indicating that bimatoprost was rapidly eliminated in all three species. The mean blood clearance was 12, 9.5 and 2.4 L/hr/kg, respectively. In mice and rats, total blood clearance appeared to be greater than liver blood flow, indicating the involvement of extrahepatic metabolism.

Systemic Tissue Distribution

The unbound fraction of bimatoprost in mouse, rat, rabbit and monkey plasma ranged from 28 to 37% *in vitro*. The *in vitro* binding of bimatoprost to synthetic melanin was not extensive at approximately 20%, and was reversible. Following intravenous administration of ^{3}H-bimatoprost to rats, either as a single dose or after daily injections for 21 days, radioactivity was rapidly distributed to all tissues and organs examined. The highest concentrations of radioactivity were seen in the gastrointestinal tract, liver, kidney and urinary bladder. The blood-to-plasma ratio of radioactivity was 0.75, indicating that bimatoprost remained in the plasma portion of the blood. By 168 hours post-dose, all radioactivity in the body was accounted for by tritiated water, and not by bimatoprost or its metabolites. Following a single intravenous administration of ^{3}H-bimatoprost to pregnant rats, there was a low, but quantifiable, amount of drug transfer into the placenta, amniotic fluid and fetus. Following intravenous administration of ^{3}H-bimatoprost to lactating rats, the concentrations of radioactivity found in milk were similar to those seen in plasma. Therefore the amount of drug related material transferred into milk at the clinical dose level is expected to be extremely low.

Ocular Metabolism

After ophthalmic administration, bimatoprost was extensively metabolized in all of the ocular tissues in the rabbit eye. In contrast, bimatoprost, at exaggerated doses, was only minimally metabolized in the monkey eye following ophthalmic administration.

Systemic Metabolism

Following a single intravenous administration to rats and monkeys, bimatoprost was extensively metabolized by glucuronidation, hydroxylation, deamidation and N-deethylation, with glucuronidated metabolites accounting for the majority of the drug-related material in the blood, urine and faeces of both species. In pregnant rats, at least 22 metabolites were detected in the maternal tissues following a single intravenous administration of ^{3}H-bimatoprost. The C1-acid metabolite of bimatoprost was the major species detected in the uterus and ovaries (about 45% of total radioactivity), while bimatoprost was the major species detected in the fetus (about 50% of total radioactivity). The C1-acid is the major metabolite in rats and rabbits, but not in dogs, monkeys, or humans. Following one month of daily intravenous administration to rats and monkeys, bimatoprost was found to have no clinically significant effect on any of the hepatic drug metabolizing enzymes tested. In studies using recombinant human P450 enzymes, CYP3A4/5 were identified as the most important Cytochrome P450 enzymes involved in the hydroxylation of bimatoprost.

Excretion

Both the urinary and fecal routes are important pathways for excretion of bimatoprost and its metabolites in rats and monkeys. Following a single intravenous administration of ^{3}H-bimatoprost to rats, the urinary excretion of radioactivity was 42% of the dose in females and 27% in males, while the faecal excretion of radioactivity was 49% in females and 69% in males. Following a single intravenous administration of ^{3}H-bimatoprost in monkeys, male and females excreted 58 and 64% of the dose into the urine and 24 and 31% into the faeces, respectively. The mean total recovery of radioactivity was >90% for both genders.

Human Pharmacology

Pharmacodynamics

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®.

Pharmacokinetics

Absorption and Systemic Drug Exposure

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 Cmax values were similar on days 7 and 14 at 0.0721, and 0.0822 ng/mL, respectively. The mean $AUC_{0\text{-}24}$ 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 $AUC_{0\text{-}24}$ 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 remain unbound in human plasma. The *in vitro* binding of bimatoprost to synthetic melanin was ~20% at concentrations of 0.2 - 100 μg/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.

Elimination

Following an intravenous dose of radiolabelled bimatoprost (3.12 μg/kg) to six healthy subjects, the maximum blood concentration of unchanged bimatoprost was 12.2 ng/mL and declined rapidly with an elimination half-life of 0.771 hour (approximately 45 minutes). Blood concentrations of AGN 191522, the C-1 acid metabolite, were much lower than those of bimatoprost as peak concentration was 0.12 ng/mL. The total blood clearance (Clb) of unchanged bimatoprost was 1.50 L/hr/kg.

Sixty-seven percent of the administered dose of bimatoprost was excreted in the urine with only a small fraction excreted as unchanged drug. Twenty-five percent of the dose was recovered in feces of which 15-40% was eliminated as unchanged drug.

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 µg in a 35 µL drop dosed once daily in both eyes - not based on the 28 µL 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.

Mutagenicity
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 μg 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 μg/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.

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.
Reproduction and Teratology

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 Toxicity Studies

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.

REFERENCES

1. Brubaker RF, Schoff EO, Nau CB, Carpenter SP, Chen K Vandenburgh AM. Effects of AGN 192024, a new ocular hypotensive agent, on aqueous dynamics. Am J Ophthalmol 2001; 131(1):19-24.

2. Dirks M, DuBiner H Cooke D et al. Efficacy and safety of the ocular hypotensive lipid AGN 192024 in patients with elevated IOP: A 30 day comparison with Latanoprost. Investigative Ophthalmol and Vis Sci1999;41(4)S514.

3. VanDenburgh AM, Laibovitz RA and Felix C. A one month dose response study of AGN 192024, a novel antiglaucoma agent in patients with elevated intraocular pressure. Investigative Ophthalmol and Vis Sci 1999;40(4):S830.

4. Woodward DF, Krauss AH-P, Chen J, Kedzie KM, Protzman CE, Shi L, Chen R, Krauss HA, Bogardus HT, Dinh T, Wheeler LA, Andrews SW, Burk RM, Gac T, Roof MB, Garst ME, Kaplan LJ, Sachs G, Pierce KL, Regan JW, Ross RA, Chan MF. Replacement of the carboxylic acid group of prostaglandin F2α with a hydroxyl or methoxy substituent provides biologically unique compounds. Br J Pharmacol 2000; 130:1933-1943.

5. Woodward DF, Fairbairn CE, Krauss A H-P, Lawrence RA, Protzman CE. Radioligand binding analysis of receptor subtypes in two FP receptor preparations that exhibit different functional rank order of a potency in response to prostaglandins. J Pharmacol Exp Ther 1995; 273(1):285-291.

PART III: CONSUMER INFORMATION

PrLUMIGAN RC®

Bimatoprost

Ophthalmic Solution 0.01% w/v

This leaflet is Part III of a three-part "Product Monograph" published when LUMIGAN RC® was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about LUMIGAN RC®. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

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

What it does:
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.

When it should not be used:
LUMIGAN RC® should not be used if you are allergic to bimatoprost, to any of the other ingredients, or to any of the parts of the container (see What the non-medicinal ingredients are).

What the medicinal ingredient is:
Bimatoprost

What the nonmedicinal ingredients are:
Benzalkonium chloride, as preservative; sodium chloride, sodium phosphate dibasic heptahydrate, citric acid monohydrate, and purified water. Sodium hydroxide and/or hydrochloric acid may be added to adjust pH.

What dosage forms it comes in:
Ophthalmic solution, 0.01%

WARNINGS AND PRECAUTIONS

This product should not be used if you have severe dry eye.

BEFORE you use **LUMIGAN RC®** talk to your doctor or pharmacist if:

- you are taking, or have recently taken, any other medicines, even those not prescribed
- you are already taking an antiglaucoma preparation as **LUMIGAN RC®** may not reduce the high pressure in the eye if used with another antiglaucoma preparation
- you are pregnant, intend to become pregnant or breastfeeding a baby. You should ask you doctor or pharmacist for advice before taking any medicine.
- you have an active eye infection or any other eye condition
- you develop another eye condition (an injury or an infection)
- you need to have eye surgery
- you are allergic to bimatoprost, to any of the other ingredients, such as benzalkonium chloride, or to any of the parts of the container

Your sight may become blurred for a short period of time just after using **LUMIGAN RC®**. Do not drive or use machines until your sight is clear again.

LUMIGAN RC® may cause your eyelashes to darken, thicken, and grow, and cause the skin around the eyelid to darken too. The color of your iris (eye) may also go darker over time. These changes may be permanent. The change may be more noticeable if you are only treating one eye. The long term effects on the eye color are unknown.

Hair may grow in areas where **LUMIGAN RC®** solution has been repeatedly in contact with the skin surface. This is why it is important to apply **LUMIGAN RC®** as instructed and to avoid it running onto the cheek or other skin areas.

INTERACTIONS WITH THIS MEDICATION

No drug interaction studies were done with **LUMIGAN RC®** and none are expected for this ophthalmic product.

PROPER USE OF THIS MEDICATION

Usual adult dose:
Normally, you should put one drop of **LUMIGAN RC®** in each eye that needs treatment, once every day, in the evening, following the instructions for use below.

You must not use the bottle if the tamper-proof seal on the bottle neck is broken before you first use it. Follow the following steps to help you use **LUMIGAN RC®** properly:

1. Wash your hands. Tilt your head back and look at the ceiling.
2. Gently pull down the lower eyelid to create a small pocket.
3. Turn the bottle upside down and squeeze it gently to release one drop into each eye that needs treatment.
4. Let go of the lower lid, and close your eye for 30 seconds.

If a drop misses your eye, try again.

LUMIGAN RC® contains a preservative called benzalkonium chloride which may discolour 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 have been prescribed LUMIGAN RC® frequently when you have a dry eye condition or damage to your cornea, your doctor may monitor your eye condition.

Always use **LUMIGAN RC®** exactly as your doctor has instructed you. If you use **LUMIGAN RC®** with another eye drop, leave at least five minutes between putting in **LUMIGAN RC®** and then 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.

Overdose:

In case of accidental oral ingestion or overdose, contact your doctor, regional poison control centre immediately or hospital emergency department, even if there are no symptoms.

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

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.**

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Very common	Occurs in more than 1 out of 10 patients
Common	Occurs in between 1 and 10 out of every 100 patients

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 doctor.

Very common
- Eye redness

Common
- Longer eyelashes
- Eye irritation
- Red and/or itchy eyelids
- Darkening of the eyelid
- Eyelash discolouration
- Itchy eyes
- Excessive hair growth
- Small breaks in the surface of the eye

Some patients (fewer than 2 in every 100) experience a change in iris color with bimatoprost treatment. The change is a darkening, with the eyes becoming more brown. This usually happens during the first year of treatment. Eye darkening is expected to increase as long as **LUMIGAN RC®** is administered.

It is not known what this change means over the long term. Talk to your doctor if you notice a change in your iris color; depending on your clinical situation your doctor may want to re-evaluate your treatment.

*This is not a complete list of side effects. For any unexpected effects while taking **LUMIGAN RC®**, contact your doctor or pharmacist.*

HOW TO STORE IT

LUMIGAN RC® should be stored in the original container at 2º to 25ºC. 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 the reach and sight of children.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to: Canada Vigilance Program
    Health Canada
    Postal Locator 1908C
    Ottawa, ON K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be obtained by contacting the sponsor, Allergan Inc, at: 1-800-668-6424

This leaflet was prepared by Allergan Inc.

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