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# DATA SHEET

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## NAME OF MEDICINE

LUMIGAN RC™ (bimatoprost) 0.01% w/v eye drops

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## Presentation

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LUMIGAN RC™ (bimatoprost) eye drops are a clear, isotonic, colourless, sterile ophthalmic solution. Bimatoprost is a white to off-white powder and is very soluble in ethyl alcohol and methyl alcohol and slightly soluble in water.

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## Uses

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### **Actions**

Pharmacotherapeutic group: Antiglaucoma preparations and miotics; prostaglandin analogues: ATC code S01EE03

Bimatoprost is a novel synthetic prostamide analogue with potent ocular hypotensive activity. It selectively mimics the effects of a newly discovered naturally occurring substance, prostamide. Prostamide is biosynthesised from anandamide by a pathway involving COX-2 but not COX-1, suggesting a new pathway that leads to the synthesis of endogenous lipid amides that lower intraocular pressure (IOP). Bimatoprost and prostamides differ from prostaglandins (PGs) in that prostamides are biosynthesized from a different precursor, anandamide; bimatoprost does not stimulate any previously described prostanoid receptor; it is not mitogenic; it does not contract the human uterus; and it is electrochemically neutral.

Bimatoprost reduces intraocular pressure in man by increasing aqueous humor outflow through the trabecular meshwork and enhancing uveoscleral outflow. Reduction of the intraocular pressure starts approximately 4 hours after the first administration and maximum effect is reached within approximately 8 to 12 hours. The duration of effect is maintained for at least 24 hours.

Clinical studies have shown mean intraocular pressure decreases of up to 8 mmHg.

### **Pharmacokinetics**

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

After once daily ocular administration of one drop of 0.03% w/v bimatoprost to both eyes of 15 healthy subjects for two weeks, blood concentrations peaked within 10 minutes after dosing and declined to below the lower limit of detection (0.025 ng/mL) within 1.5 hours after dosing. Mean bimatoprost  $C_{max}$  values were similar on days 7 and 14 at 0.0721 and 0.0822 ng/mL respectively. The mean  $AUC_{0-24hr}$  values were also similar on days 7 and 14 at 0.0742 and 0.096ng.hr/mL respectively, indicating that a steady systemic exposure to bimatoprost was reached during the first week of ocular dosing. The systemic exposure of bimatoprost is very low with no accumulation over time.

Bimatoprost is moderately distributed into body tissues with a steady state systemic volume of distribution in humans of 0.67 L/kg. In human blood, bimatoprost resides mainly in the plasma. The plasma protein binding of bimatoprost is approximately 90%.

Data from *in vitro* studies showed that the overall extent of melanin binding was not dependent on concentration and the binding was reversible.

Bimatoprost is the major circulating species in the blood once it reaches the systemic circulation following ocular dosing in humans. Bimatoprost then undergoes oxidation, N-deethylation and glucuronidation to form a diverse variety of metabolites.

Bimatoprost is eliminated primarily by renal excretion. Up to 67% of an intravenous dose of radiolabelled bimatoprost administered to healthy volunteers was excreted in the urine, 25% of the dose was excreted via the faeces. The elimination half-life, determined after intravenous administration, was approximately 45 minutes, the total blood clearance of unchanged bimatoprost was 1.5 L/hr/kg.

After twice daily dosing, with bimatoprost 0.03% w/v the mean AUC<sub>0-24hr</sub> value of 0.0634 ng.hr/mL for bimatoprost in the elderly (subjects 65 years or older) was statistically significantly higher than that of 0.0218 ng.hr/mL in young healthy adults, suggesting the existence of an age effect. However, this finding is not clinically relevant as systemic exposure for elderly and young subjects remained very low from ocular dosing. There was no accumulation of bimatoprost in the blood over time and the safety profile was similar in elderly and young patients.

### **Indications**

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

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## **Clinical Studies**

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Elevated IOP presents a major risk factor in the pathogenesis of glaucomatous visual field loss. The higher the level of intraocular pressure, the greater the likelihood of optic nerve damage and glaucomatous visual field loss. Bimatoprost has the action of lowering intraocular pressure with no clinically relevant effects on heart rate and blood pressure observed in clinical trials.

In a 12 month pivotal study of 561 patients LUMIGAN RC™ 0.01% w/v eye drops was shown to be an effective IOP lowering therapy. Overall 89.8%(504/561) of patients completed the study up to and including the 12 month visit of which 186 patients received LUMIGAN RC™ 0.01% w/v. Bimatoprost 0.03 % w/v and LUMIGAN RC™ were administered QD to each eye. Two primary efficacy endpoints were evaluated:

**mean IOP** at all timepoints up to and including the month 3 visit assessed using an equivalence analysis.

**mean change from baseline IOP** assessed by combined tests of non-inferiority and superiority at each post-baseline timepoint.

#### **Primary Analysis for Mean IOP:**

LUMIGAN RC™ was equivalent to LUMIGAN® (bimatoprost 0.03% w/v) for mean IOP at 12 months.

**Primary Analysis for Mean Change from Baseline IOP:** All treatments studied showed statistically and clinically significant mean decreases from baseline at all follow up timepoints ( $p < 0.001$ ). By Month 12, LUMIGAN RC™ was non-inferior to LUMIGAN® at 15/17 timepoints.

Over the 12 months, the efficacy of LUMIGAN RC™ was maintained. Mean IOP and mean change from baseline IOP, at peak and trough, were significantly decreased with LUMIGAN RC™, showing a sustained therapeutic effect.

<b>LUMIGAN RC™ Study 1 (N=186)</b>							
	<b>Baseline</b>	<b>Week 2</b>	<b>Week 6</b>	<b>Month 3</b>	<b>Month 6</b>	<b>Month 9</b>	<b>Month 12</b>
<b>Mean Intraocular Pressure (mm Hg)</b>							
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
<b>Mean Change from Baseline Intraocular Pressure (mm Hg)</b>							
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*

**Mean IOP and Mean Change from Baseline IOP (mm Hg) at Each Timepoint for LUMIGAN RC™ in Study 1**

\* statistically significant change from baseline ( $p < 0.001$ ); NA= Not Applicable

Secondary analysis of mean diurnal IOP was also positive with LUMIGAN RC™ being non-inferior to bimatoprost 0.03% w/v at all post-baseline timepoints. Clinical studies have also demonstrated that bimatoprost is effective when used in combination with beta-blockers.

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## **Dosage and Administration**

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**Monotherapy:** The recommended dose is one drop of LUMIGAN RC™ in the affected eye(s) once daily, administered in the evening.

**Adjunctive Therapy:** The recommended dose is one drop of LUMIGAN RC™ in the affected eye(s) once daily, administered in the evening.

More frequent administration has not been shown to provide increased efficacy.

If more than one topical ophthalmic medication is to be used, the other medication should not be used within 5 minutes of using LUMIGAN RC™ eye drops.

In order to minimise systemic absorption of LUMIGAN RC™ eye drops, patients should be instructed to apply pressure to the tear duct immediately following administration of the drug.

### ***Paediatric Use***

Safety and effectiveness in patients below 18 years of age have not been established.

### ***Use in Elderly***

No dosage adjustment in elderly patients is necessary.

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## Contraindications

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LUMIGAN RC™ eye drops are contraindicated in patients with hypersensitivity to bimatoprost or to any component of the medication.

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## Warnings and Precautions

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### **General:**

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

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

During treatment with bimatoprost eye drops, darkening of the eyelid skin and gradual increased eyelash growth (lengthening, darkening and thickening) with no consequent untoward ocular effects have been observed. Increased iris pigmentation has also been reported. The change in iris pigmentation occurs slowly and may not be noticeable for several months. At 12 months, there was one report of iris hyperpigmentation with bimatoprost 0.01% w/v eye drops (incidence of 0.5%). At 12 months, the incidence with bimatoprost 0.03% w/v eye drops was 1.5% and did not increase following 3 years treatment.

Before treatment is initiated, patients should be informed of the possibility of eyelash growth, darkening of the eyelid skin and increased iris pigmentation with LUMIGAN RC™. Some of these changes may be permanent and may lead to differences in appearance between the eyes when only one eye is treated.

LUMIGAN RC™ has not been studied in patients with inflammatory ocular conditions, neovascular, inflammatory, angle-closure glaucoma, congenial glaucoma or narrow angle glaucoma.

Limited experience is available with the use of LUMIGAN RC™ in patients with open-angle glaucoma with pseudoexfoliative and pigmentary glaucoma, and chronic angle-closure glaucoma with patent iridotomy.

Cystoid macular oedema has been uncommonly reported ( $\geq 1/1000$  to  $<1/100$ ) following treatment with bimatoprost 0.03% w/v eye drops, solution. Therefore, LUMIGAN RC™ should be used with caution in patients with known risk factors for macular oedema (e.g. aphakic patients, pseudophakic patients with a torn posterior lens capsule).

### **Preclinical Findings:**

Ocular administration of bimatoprost in monkeys at concentrations of 0.03% w/v or 0.1% w/v once or twice daily for 1 year caused an increase in iris pigmentation and reversible dose-related periocular effects characterised by a prominent upper and/or lower sulcus and widening of the palpebral fissure. No associated increase in melanocyte number was observed with the pigmentation. It appears that the mechanism of increased iris pigmentation is due to increased stimulation of melanin production in melanocytes and not to an increase in melanocyte number.

Periocular effects were also observed in an intravenous toxicity study at systemic exposures at least 235-fold higher than that observed in humans after ocular administration. No functional or microscopic changes related to the periocular effects were observed. The mechanism of action for the observed periocular changes is unknown.

### ***Carcinogenicity and Mutagenicity:***

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

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

### ***Impairment of Fertility:***

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

### ***Pregnancy and Lactation:***

Pregnancy Category B3: There are no adequate and well-controlled studies in pregnant women.

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

LUMIGAN RC™ should not be used during pregnancy unless clearly necessary.

### ***Use in Lactation***

Bimatoprost was excreted in rat milk following PO administration. Increased pup mortality and depressed pup growth occurred when dams were treated PO with bimatoprost from gestation day 7 to lactation day 20 at  $\geq 0.3$  mg/kg/day, corresponding to exposures approximately 41 times the expected human exposure.

There are no data on the excretion of bimatoprost into human milk or on the safety of bimatoprost exposure in infants. Because many drugs are excreted in human milk, nursing women who use LUMIGAN RC™ should stop breast feeding.

### ***Effects on ability to drive and use machines:***

LUMIGAN RC™ has negligible influence on the ability to drive and use machines. As with any ocular treatment, if transient blurred vision occurs at instillation, the patient should wait until the vision clears before driving or using machinery.

### ***Information for patients:***

LUMIGAN RC™ eye drops contain the preservative benzalkonium chloride, which may be absorbed by soft contact lenses. Contact lenses should be removed prior to instillation of LUMIGAN RC™ and may be reinserted 15 minutes following administration. LUMIGAN RC™ should not be administered while wearing contact lenses.

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## Adverse Effects

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In a 12 month clinical study approximately 38% of patients treated with LUMIGAN RC™ 0.01% w/v eye drops experienced undesirable effects considered related to treatment. The most frequently reported treatment-related adverse event was conjunctival hyperaemia (mostly trace to mild and thought to be of a non-inflammatory nature) occurring in 29% of patients compared to 42% being the previously reported rate from the bimatoprost 0.03% w/v LUMIGAN® registration trials. The treatment related ocular events was 37.8% with LUMIGAN RC™ compared to 50.3% with LUMIGAN® (p=0.016). Approximately 4% of patients in the LUMIGAN RC™ trial discontinued due to any adverse event over the 12-month study compared with less than 8% of patients with LUMIGAN®.

The following undesirable effects considered related to treatment were reported during clinical trials with LUMIGAN RC™ eye drops. Most were ocular, mild and none was serious.

With each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

### *Nervous system disorders*

Uncommon (<1%): Headache

### *Eye disorders*

Very common (>10%): Conjunctival hyperaemia

Common (<10%): Punctate keratitis, eye irritation, eye pruritus, growth of eyelashes

Uncommon (≤1%): Asthenopia, conjunctival disorder, conjunctival oedema, iris hyperpigmentation, madarosis, vision blurred

### *Gastrointestinal disorders*

Uncommon, (≤1%): Nausea

### *Skin and subcutaneous tissue disorders*

Common (<10%): Erythema of eyelid, eyelids Pruritus, skin hyperpigmentation, hypertrichosis

Uncommon(≤1%): Dry skin, eyelid margin crusting, eyelid oedema, pruritus

### *General disorders and administration site conditions*

Common (<10%): Instillation site irritation

The following undesirable effects definitely, probably or possibly related to treatment were reported during clinical trials with bimatoprost 0.03% w/v eye drops. Most were ocular, mild to moderate, and none was serious:

*Ocular effects:* Conjunctival hyperaemia, growth of eyelashes, ocular pruritus, allergic conjunctivitis, asthenopia, blepharitis, conjunctival oedema, corneal erosion, eye discharge, eyelash darkening, eyelid erythema, eyelid pruritus, eye pain, foreign body sensation, increased iris pigmentation, ocular burning, ocular dryness, ocular irritation, photophobia, pigmentation of periocular skin, superficial punctate keratitis, tearing, visual disturbance,

worsening of visual acuity, blepharospasm, eyelid oedema, eyelid retraction, iritis, retinal haemorrhage.

*Systemic effects:*

Body as a whole

Asthenia, headache, infection (primarily colds and upper respiratory tract infections).

Nervous system effects

Depression, vertigo.

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## Interactions

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No drug-drug interactions are anticipated in humans since systemic concentrations of bimatoprost are extremely low (less than 0.2 ng/mL) following ocular dosing with bimatoprost 0.03% w/v eye drops. No effects on hepatic drug metabolising enzymes were observed in pre-clinical studies. Therefore, specific interaction studies with other medicinal products have not been performed with LUMIGAN RC™.

In clinical studies, bimatoprost 0.03% w/v eye drops was used concomitantly with a number of different ophthalmic beta-blocking agents without evidence of drug interaction.

Concomitant use of LUMIGAN RC™ and anti-glaucoma agents other than topical beta-blockers has not been evaluated during adjunctive glaucoma therapy.

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## Overdosage

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If overdosage occurs, treatment should be symptomatic and supportive.

Ophthalmic overdose: No case of overdose has been reported, and is unlikely to occur after ocular administration.

If overdosage occurs, treatment should be symptomatic and supportive. If LUMIGAN RC™ is accidentally ingested, the following information may be useful: in two-week oral rat and mouse studies, doses up to 100 mg/kg/day did not produce any toxicity. This dose expressed as mg/m<sup>2</sup> is at least 210-times higher than the accidental dose of one 3 mL bottle of LUMIGAN RC™ 0.01% w/v eye drops in a 10 kg child.

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## Pharmaceutical Precautions

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To avoid contamination of the solution, keep container tightly closed. Do not touch dropper tip to any surface. Contents are sterile if seal is intact.

Shelf life: 2 years

Storage: Store below 25°C

Discard contents 4 weeks after opening the bottle.

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## Medicine Classification

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Prescription Medicine

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## Package Quantities

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LUMIGAN RC™ (bimatoprost) 0.01% w/v eye drops are supplied in plastic dropper bottles with a plastic screw cap. Each bottle has a fill volume of 3 mL.

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## Further Information

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### *List of excipients*

PRESERVATIVE: benzalkonium chloride

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

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## Name and Address

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Allergan New Zealand Ltd,  
Cnr Manu Tapu Drive & Joseph Hammond Place,  
Auckland International Airport, Mangere,  
Auckland, NEW ZEALAND  
Toll free telephone: 0800 659 912

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## Date of Preparation

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February 2010