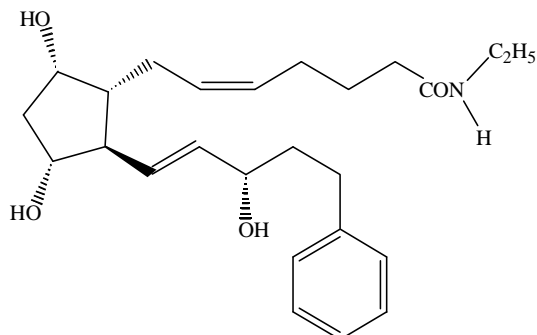


LUMIGAN[®] Eye Drops

NAME OF THE DRUG

The active constituent of LUMIGAN[®] eye drops is bimatoprost.

Chemical structure:



Chemical name:

(Z)-7-[(1R,2R,3R,5S)-3,5-Dihydroxy-2-[(1E,3S)-3-hydroxy-5-phenyl-1-pentenyl]cyclopentyl]-N-ethyl-5-heptenamide

Molecular weight: 415.58

Empirical formula: C₂₅H₃₇NO₄

CAS Registry No.: 155206-00-1

DESCRIPTION

Bimatoprost (LUMIGAN[®] eye drops 0.3mg/mL) is a prostamide with potent ocular hypotensive activity. Bimatoprost is a white to off-white powder and is very soluble in ethyl alcohol and methyl alcohol and slightly soluble in water. LUMIGAN[®] is a clear, isotonic, colourless, sterile ophthalmic solution with an osmolality of approximately 290mOsmol/kg.

LUMIGAN[®] 0.3mg/mL is a sterile ophthalmic solution. Each mL of LUMIGAN[®] solution contains:

ACTIVE: bimatoprost 0.3 mg

PRESERVATIVE: benzalkonium chloride 0.05 mg

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

PHARMACOLOGY

Mechanism of action

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 humour outflow through the trabecular meshwork and enhancing uveoscleral outflow. Reduction of the intraocular pressure starts approximately 4 hours after the first administration and maximum effect is reached within approximately 8 to 12 hours. The duration of effect is maintained for at least 24 hours.

Clinical studies have shown mean intraocular pressure decreases of up to 9 mmHg.

Pharmacokinetics

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

After once daily ocular administration of one drop of 0.03% bimatoprost to both eyes of 15 healthy subjects for two weeks, blood concentrations peaked within 10 minutes after dosing and declined to below the lower limit of detection (0.025 ng/mL) within 1.5 hours after dosing. Mean bimatoprost C_{max} values were similar on days 7 and 14 at 0.0721 and 0.0822 ng/mL respectively. The mean AUC_{0-24hr} 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 radiolabeled bimatoprost administered to healthy volunteers was excreted in the urine, 25% of the dose was excreted via the faeces. The elimination half-life, determined after intravenous administration, was approximately 45 minutes, the total blood clearance of unchanged bimatoprost was 1.5 L/hr/kg.

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

CLINICAL STUDIES

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.

Monotherapy

The efficacy of LUMIGAN[®] eye drops was demonstrated in two multi-centre studies compared with timolol 0.5% after 6 months treatment in subjects with chronic glaucoma or ocular hypertension. In each, both once daily and twice daily bimatoprost was compared to twice daily timolol 0.5%. A total of 1198 patients were enrolled in the two studies with 474 receiving bimatoprost once daily, 483 receiving bimatoprost twice daily and 241 receiving timolol.

Table 1: Intraocular Pressure (mm Hg) ± SD in Individual Phase 3 Monotherapy Studies: Mean Baseline and Mean Changes from Baseline at Month 6

timepoint visit	Study 1			Study 2		
	Bimatoprost QD (N = 240)	Bimatoprost BID (N = 240)	timolol (N = 122)	Bimatoprost QD (N = 234)	Bimatoprost BID (N = 243)	timolol (N = 119)
Hour 0						
baseline	25.85±3.18	26.10±3.06	25.82±2.94	26.05±3.28	25.59±3.15	25.71±3.31
month 6	-7.88 ^a ±3.69	-7.00 ^b ± 3.85	-6.27±3.48	-8.69 ^a ±3.96	-7.30 ^b ±3.71	-6.63±3.65
Hour 2						
baseline	24.64±3.86	24.80±3.95	24.01±3.64	24.70±3.51	24.39±3.49	24.11±3.44
month 6	-7.59 ^a ± 4.47	-6.00 ^b ±4.36	-5.29±3.93	-8.59 ^a ±3.60	-6.64 ^b ±3.88	-5.96±3.78
Hour 8						
baseline	23.87±3.99	23.92±4.18	23.16±3.88	23.73±3.79	23.44±3.76	23.30±3.86
month 6	-6.88 ^a ±4.28	-5.55 ^a ±4.46	-4.17±3.96	-7.14 ^a ±3.94	-6.14 ^a ±3.77	-4.96±3.80

a Bimatoprost superior to timolol (p ≤ 0.05); b Bimatoprost non-inferior to timolol.; N = number of patients at baseline

LUMIGAN[®] eye drops administered once daily as monotherapy, have consistently shown clinically and statistically superior IOP reduction vs timolol 0.5% twice daily over a six month period. Mean IOP changes from baseline for LUMIGAN[®] once daily ranged from 6.88 to 7.88 mmHg in study 1 and 7.14 to 8.69 mmHg in study 2. These were superior to the decreases seen in the timolol group (4.17 to 6.27 mmHg and 4.96 to 6.63 mmHg respectively). Twice daily dosing did not show any increased efficacy compared to once daily dosing.

In addition to mean change from baseline, a frequency analysis of the IOP recorded at hour 0 at each visit was performed. In the two studies 46% and 52.5% of patients achieved an

IOP of 17 mmHg or less (a commonly agreed ‘target IOP’) with bimatoprost once daily over the time period studied, compared to 25.4% and 29% in the timolol group. These results corroborate the statistical and clinical superiority of the once daily regimen over timolol seen at all visits.

Adjunctive Therapy

The ability of LUMIGAN® 0.03% eye drops to lower IOP when used as adjunctive therapy to topical beta-blocker monotherapy has been evaluated in two large scale multi-centre, randomised 3 month studies, involving 722 patients of which 489 received bimatoprost. The numbers and proportions of the different topical beta-blocking agents used in the studies were representative of clinical practice.

Table 2: Intraocular Pressure (mm Hg) ± SD in Individual Phase 3 Adjunctive Studies: Mean Baseline and Mean Changes from Baseline at Month 3

timepoint visit	Study 1			Study 2		
	Bimatoprost QD/BB (N = 153)	Bimatoprost BID/BB (N = 146)	Latanoprost/BB (N = 138)	Bimatoprost QD/BB (N = 93)	Bimatoprost BID/BB (N = 97)	Vehicle/BB (N = 95)
Hour 0						
baseline	25.02±2.95	24.99±2.51	25.17±2.97	24.51±2.50	24.64±2.76	24.40±2.90
month 3	-7.95 ^b ±3.81	-7.26 ^b ± 3.48	-7.35±3.74	-7.38 ^a ±4.72	-6.34 ^a ±3.86	-3.59±3.46
Hour 2						
baseline	23.18±3.68	23.11±3.62	23.32±3.34	22.22±3.35	22.25±3.86	21.54±3.46
month 3	-7.03 ^b ±3.99	-5.33±4.09	-6.39±3.92	-6.45 ^a ±4.20	-4.73 ^a ±4.07	-2.29±3.65
Hour 8						
baseline	22.42±3.90	22.36±4.03	23.05±3.67	21.96±3.04	22.15±3.99	21.44±3.48
month 3	-6.03 ^b ±4.15	-4.64±4.25	-5.89±3.91	-6.39 ^a ±3.77	-4.45 ^a ±4.23	-2.62±3.64

a Bimatoprost superior to vehicle/timolol ($p \leq 0.001$); b Bimatoprost non-inferior to latanoprost/BB.; N = number of patients at baseline; BB=beta-blocker

Overall at month 3 in study 1, the mean decreases from baseline IOP at hours 0, 2 and 8 in patients treated with LUMIGAN® once daily/beta-blocker ranged from 6.03 to 7.95 mmHg. These were non-inferior to the decreases seen in the latanoprost/beta-blocker group (5.89 to 7.35 mmHg) at all time points.

Overall at month 3 in study 2, the mean decreases from baseline IOP at hours 0, 2 and 8 in patients treated with LUMIGAN® once daily/beta-blocker ranged from 6.39 to 7.38 mmHg. These were superior to the decreases seen in the vehicle/beta-blocker group (2.62 to 3.59 mmHg) at all time points. LUMIGAN® once daily/beta-blocker showed superiority to vehicle/beta-blocker at all time points at all visits.

INDICATIONS

LUMIGAN® is indicated for the reduction of elevated intraocular pressure, or open angle glaucoma, as first line therapy or monotherapy or as adjunctive therapy to topical beta-blockers.

CONTRAINDICATIONS

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

PRECAUTIONS

General:

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

During treatment with LUMIGAN®, 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. The effect has been seen in up to 2% of patients treated with LUMIGAN® for up to 6 months. Before treatment is initiated, patients should be informed of the possibility of eyelash growth, darkening of the eyelid skin and increased iris pigmentation. Some of these changes may be permanent and may lead to differences in appearance between the eyes when only one eye is treated.

Drug Interactions:

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

In clinical studies, LUMIGAN® was used concomitantly with a number of different ophthalmic beta-blocking agents without evidence of drug interactions.

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

Preclinical Findings:

Ocular administration of bimatoprost in monkeys at concentrations of 0.03% or 0.1% once or twice daily for 1 year caused an increase in iris pigmentation and reversible dose-related periocular effects characterised by a prominent upper and/or lower sulcus and widening of the palpebral fissure. No associated increase in melanocyte number was observed with the pigmentation. It appears that the mechanism of increased iris pigmentation is due to

increased stimulation of melanin production in melanocytes and not to an increase in melanocyte number.

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

Carcinogenicity and Mutagenicity:

Long-term studies in mice and rats revealed no evidence of carcinogenicity following oral (by gavage) administration of bimatoprost at doses up to 2 and 1 mg/kg/day, respectively. These doses resulted in systemic bimatoprost levels 85 – 95 times the maximum anticipated human exposure (based on blood AUC). In the rat carcinogenicity study, a dose-related increase in vacuolated corpora lutea was observed. The clinical relevance of this ovarian effect is unclear.

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 corresponding to 30 – 50 times the expected human exposure (based on blood AUC calculated from total blood concentration).

Use in Pregnancy: Category B3

Bimatoprost and/or its metabolites crossed the placenta in rats. In embryo/foetal developmental studies in pregnant mice and rats, abortion was observed at oral doses of bimatoprost of 0.3 and 0.6 mg/kg/day, respectively, resulting in exposures 15 and 34 times the expected human exposure (based on blood AUC calculated from total blood concentration). Bimatoprost was not teratogenic at up to 0.6 mg/kg/day in mice or rats. At doses of ≥ 0.3 mg/kg/day PO in rats, approximately 20 times the expected human exposure, the gestation length was reduced, embryofoetal losses and peri- and postnatal pup mortality were increased, and pup body weights were reduced.

There are no adequate and well-controlled studies in pregnant women. LUMIGAN[®] should not be used during pregnancy unless clearly necessary.

Use in Lactation:

Bimatoprost was excreted in rat milk following PO administration. Increased pup mortality and depressed pup growth occurred when dams were treated PO with bimatoprost from gestation day 7 to lactation day 20 at ≥ 0.3 mg/kg/day, corresponding to exposures approximately 20 times the expected human exposure (based on blood AUC calculated from total blood concentration).

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[®] should stop breast feeding.

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.

Information for patients:

LUMIGAN® 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® and may be reinserted 15 minutes following administration. LUMIGAN® should not be administered while wearing contact lenses.

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

ADVERSE REACTIONS

In clinical studies, over 1,700 patients have been treated with LUMIGAN®.

In the two pivotal monotherapy trials (715 patients) the most frequently reported treatment-related adverse events were: conjunctival hyperemia in up to 42%, growth of eyelashes in up to 36% and ocular pruritus in up to 14% of patients. The incidence of conjunctival hyperemia at baseline was 25.1% and 17.8% in patients allocated to treatment with LUMIGAN® once daily and timolol twice daily, respectively. At 6 months, the incidence of patients with a greater than mild increase in conjunctival hyperemia was 6.2% and 0.4% in patients treated with LUMIGAN® once daily and timolol twice daily, respectively. Less than 7% of patients discontinued due to any adverse event.

The following undesirable effects definitely, probably or possibly related to treatment were reported during clinical trials with LUMIGAN®. Most were ocular, mild to moderate, and none was serious:

Ocular effects:

Very common (>10%): conjunctival hyperemia, growth of eyelashes, ocular pruritus.

Common (<10%): allergic conjunctivitis, asthenopia, blepharitis, conjunctival oedema, corneal erosion, eye discharge, eyelash darkening, eyelid erythema, eyelid pruritus, eye pain, foreign body sensation, increased iris pigmentation, ocular burning, ocular dryness, ocular irritation, photophobia, pigmentation of periocular skin, superficial punctate keratitis, tearing, visual disturbance and worsening of visual acuity.

Uncommon (<1%): blepharospasm, eyelid oedema, eyelid retraction, iritis, retinal hemorrhage.

Systemic effects:*Body as a whole*

Common: asthenia, headache

Uncommon: infection (primarily colds and upper respiratory tract infections).

Nervous system effects

Uncommon: depression, vertigo.

DOSAGE AND ADMINISTRATION

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

Adjunctive Therapy: The recommended dose is one drop of LUMIGAN® 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® eye drops.

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

To avoid contamination of the solution, keep container tightly closed. Do not touch dropper tip to any surface. Discard contents 4 weeks after opening the bottle. Contents are sterile if seal is intact.

OVERDOSAGE

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.

Systemic overdose resulting from accidental ingestion: If LUMIGAN® is accidentally ingested, the following information may be useful: in two-week oral rat and mouse studies, doses up to 250 mg/kg/day did not produce any toxicity. This dose expressed as mg/kg is 1,100 times higher than the accidental dose of one bottle (7.5mL) of LUMIGAN® in a 10 kg child.

PRESENTATION:

LUMIGAN® (bimatoprost) 0.3mg/mL eye drops sterile solution is supplied in plastic dropper bottles with a plastic screw cap. Each bottle has a fill volume of 3 mL, 5 mL or 7.5 mL.

LUMIGAN® eye drops have a shelf life of 2 years. Store below 25°C. Discard contents 4 weeks after opening the bottle.

POISONS SCHEDULE: S4, prescription only medicine

AUST R 80657

SPONSOR NAME AND ADDRESS

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