1. NAME OF THE MEDICINE

LUMIGAN 0,01 % m/v eye drops, solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of sterile solution contains bimatoprost 0,1 mg.

Excipient with known effect

Contains benzalkonium chloride 0,02 % m/v as a preservative.

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Eye drops, solution.

Clear colourless solution with no foreign particles.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Reduction of elevated intraocular pressure in chronic open-angle glaucoma and ocular hypertension (as monotherapy or as adjunctive therapy to beta-blockers).

4.2 Posology and method of administration

Posology

When used as monotherapy or as adjunctive therapy, the recommended dose is one drop of LUMIGAN 0,01 % in the affected eye(s) once daily, administered in the evening. The dose should not exceed once daily as more frequent administration may lessen the intraocular pressure lowering effect.

Special populations

Elderly population

No dosage adjustment in elderly patients is necessary.

Patients with hepatic and renal impairment

LUMIGAN 0,01 % has not been studied in patients with renal or moderate to severe hepatic impairment and should therefore be used with caution in such patients. In patients with a history of mild liver disease or abnormal ALT, AST and/or bilirubin at baseline, bimatoprost 0,03 % had no adverse effect on liver function over 24 months.

Paediatric population

LUMIGAN 0,01 % has only been studied in adults and therefore its use is not recommended in children or adolescents (under the age of 18).

Method of administration

To prevent contamination of the dropper tip and solution, care should be taken not to touch the eyelids, surrounding areas or other surfaces with the dropper tip of the bottle (see section 4.4).

If more than one topical ophthalmic medicine is being used, the medicines should be administered at least 5 minutes apart.

4.3 Contraindications

Hypersensitivity to bimatoprost or to any of the excipients listed in section 6.1.

LUMIGAN 0,01 % is contraindicated in patients who have had a suspected previous adverse reaction to benzalkonium chloride that has led to discontinuation.

4.4 Special warnings and precautions for use

Ocular

Before treatment is initiated, patients should be informed of the possibility of prostaglandin analogue periorbitopathy (PAP) and increased iris pigmentation, since these have been observed during treatment with LUMIGAN 0,01 %. Some of these changes may be permanent and may lead to

impaired field of vision and differences in appearance between the eyes when only one eye is treated (see section 4.8).

Patients should be informed of the possibility of eyelash growth since this has been observed during treatment with prostaglandin analogues, including LUMIGAN 0,01 %.

Increased iris pigmentation has occurred when LUMIGAN 0,01 % has been administered. Patients should be advised about the potential for increased brown iris pigmentation which is likely to be permanent (see section 4.8).

Macular oedema, including cystoid macular oedema, has been reported following treatment with bimatoprost 0,03 % eye drops, solution for elevated IOP. LUMIGAN 0,01 % 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 oedema (e.g. intraocular surgery, retinal vein occlusions, ocular inflammatory disease and diabetic retinopathy).

LUMIGAN 0,01 % should be used with caution in patients with active intraocular inflammation (e.g. uveitis) because the inflammation may be exacerbated.

There have been rare spontaneous reports of reactivation of previous corneal infiltrates or ocular infections with bimatoprost 0,03 % eye drops, solution. LUMIGAN 0,01 % should be used with caution in patients with a prior history of significant ocular viral infections (e.g. herpes simplex) or uveitis/iritis.

LUMIGAN 0,01 % has not been studied in patients with inflammatory ocular conditions, neovascular, inflammatory, angle-closure glaucoma, congenital glaucoma or narrow-angle glaucoma.

Skin

Bimatoprost ophthalmic solution has been reported to cause changes to

pigmented tissues. When bimatoprost 0,03 % (multi-dose) was instilled directly into the eye (for treatment of elevated IOP), the most frequently reported pigmentary changes have been increased pigmentation of periorbital tissue (eyelid), eyelashes and the iris.

There is the potential for hair growth to occur in areas where LUMIGAN 0,01 % solution comes repeatedly in contact with the skin surface. Thus, it is important to apply LUMIGAN 0,01 % as instructed and to avoid it running onto the cheek or other skin areas.

Respiratory
LUMIGAN 0,01 % has not been studied in patients with compromised respiratory function and should therefore be used with caution in such patients. While there is limited information available on patients with a history of asthma or COPD, there have been reports of exacerbation of asthma, dyspnoea and COPD, as well as reports of asthma, in post-marketing experience. The frequency of these symptoms is not known. Patients with COPD, asthma or compromised respiratory function due to other conditions should be treated with caution.

Cardiovascular
LUMIGAN 0,01 % has not been studied in patients with heart block more severe than first degree or uncontrolled congestive heart failure. There have been a limited number of spontaneous reports of bradycardia or hypotension with bimatoprost 0,03 % eye drops, solution. LUMIGAN 0,01 % should be used with caution in patients predisposed to low heart rate or low blood pressure.

Other Information
In bimatoprost 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 (see section 4.5). Patients using LUMIGAN 0,01 % with other prostaglandin

analogues should be monitored for changes to their intraocular pressure.

LUMIGAN 0,01 % contains the preservative benzalkonium chloride, which may be absorbed by soft contact lenses. Eye irritation and discolouration of the soft contact lenses may also occur because of the presence of benzalkonium chloride. Contact lenses should be removed prior to instillation and may be reinserted 15 minutes following administration.

Benzalkonium chloride (BAK), which is commonly used as a preservative in ophthalmic products, has been reported to cause punctate keratopathy and/or toxic ulcerative keratopathy. Since LUMIGAN 0,01 % contains benzalkonium chloride, it should be used with caution in dry eye patients, in patients where the cornea may be compromised and in patients taking multiple BAK-containing eye drops. In addition, monitoring is required with prolonged use in such patients.

Due to the possibility of corneal permeability and the danger of disruption of the corneal epithelium with prolonged or repeated usage of benzalkonium chloride, regular ophthalmological examinations are required.

Caution should be exercised in the use of benzalkonium chloride over an extended period in patients with extensive ocular surface disease.

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 ocular disease. Patients with a disruption of the ocular epithelial surface are at greater risk of developing bacterial keratitis.

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.

4.5 Interaction with other medicines and other forms of interaction

No interaction studies have been performed.

Bimatoprost is biotransformed by multiple enzymes and pathways, and no effects on hepatic medicine metabolising enzymes were observed in pre-clinical studies.

In clinical studies, bimatoprost 0,03 % eye drops (multi-dose) was used concomitantly with a number of different ophthalmic beta-blocking agents without evidence of medicine interactions.

Concomitant use of LUMIGAN 0,01 % and anti-glaucoma agents other than topical beta-blockers has not been evaluated during adjunctive glaucoma therapy.

There is a potential for the IOP-lowering effect of prostaglandin analogues (e.g. LUMIGAN 0,01 %) to be reduced in patients with glaucoma or ocular hypertension when used with other prostaglandin analogues (see section 4.4).

4.6 Fertility, pregnancy and lactation

The safety of LUMIGAN 0,01 % during pregnancy and lactation has not been established.

Pregnancy

LUMIGAN 0,01 % should not be used during pregnancy unless clearly necessary.

Breastfeeding

It is not known whether LUMIGAN 0,01 % is excreted in human milk, although in animal studies, bimatoprost has been shown to be excreted in breast milk. It is recommended that it not be used in breastfeeding mothers.

4.7 Effects on ability to drive and use machines

If transient blurred vision occurs at instillation, the patient should wait until the vision clears before driving or using machinery.

4.8 Undesirable effects

Summary of the safety profile

In clinical studies with LUMIGAN 0,01 % the most common adverse event was conjunctival hyperaemia (29 %). Approximately 1,6 % of patients discontinued therapy due to conjunctival hyperaemia with LUMIGAN 0,01 % eye drops.

Tabulated summery of adverse reactions

The following side effects were reported during clinical trials or in the post-marketing period with LUMIGAN 0,01 % and were considered to be treatment related.

The frequency is defined as follows: Very Common (≥ 1/10); Common (≥1/100 to <1/10); Uncommon (≥ 1/1 000 to < 1/100); Rare (≥ 1/10 000 to < 1/1 000); Very Rare (< 1/10 000); Not known (cannot be estimated from available data).

Table 1

System organ class	**Frequency**	**Adverse reaction**
Nervous system disorders	Uncommon	Headache
	Not known	Dizziness
Eye disorders	Very common	Ocular/conjunctival hyperaemia, prostaglandin analogue periorbitopathy
	Common	Punctate keratitis, eye irritation, eye pruritus, growth of eyelashes, eye pain, erythema of eyelid, eyelid pruritus
	Uncommon	Asthenopia, blurred vision, conjunctival disorder, conjunctival oedema, iris hyperpigmentation, madarosis
	Not known	Blepharal pigmentation, macular oedema,

		dry eye, eye discharge, eye oedema, foreign body sensation in eyes, lacrimation increased, ocular discomfort, photophobia, eyelid oedema
Respiratory, thoracic and mediastinal disorders	Not known	Asthma, asthma exacerbation, COPD exacerbation, dyspnoea
Gastro-intestinal disorders	Uncommon	Nausea
Skin and subcutaneous tissue disorders	Common	Skin hyperpigmentation, abnormal hair growth around the eyes (hypertrichosis),
	Uncommon	Dry skin, eyelid margin crusting, pruritus
	Not known	Skin discolouration (periocular)
General disorders and administration site conditions	Common	Instillation site irritation
Immune system disorders	Not known	Hypersensitivity reaction including signs and symptoms of eye allergy and allergic dermatitis
Vascular disorders	Not known	Hypertension

Description of selected adverse reactions

Prostaglandin analogue periorbitopathy (PAP)

Prostaglandin analogues including LUMIGAN 0,01 % can induce periorbital lipodystrophic changes which can lead to deepening of the eyelid sulcus, ptosis, enophthalmos, eyelid retraction, involution of dermatochalasis and inferior scleral show. Changes are typically mild, can occur as early as one month after initiation of treatment with LUMIGAN 0,01 %, and may cause impaired field of vision even in the absence of patient recognition. PAP is also

associated with periocular skin hyperpigmentation or discolouration and hypertrichosis. All changes have been noted to be partially or fully reversible upon discontinuation or switch to alternative treatments.

Iris hyperpigmentation

Increased iris pigmentation is likely to be permanent. The pigmentation change is due to increased melanin content in the melanocytes rather than to an increase in the number of melanocytes. The long-term effects of increased iris pigmentation are not known. Iris colour changes seen with ophthalmic administration of LUMIGAN 0,01 % may not be noticeable for several months to years. Typically, the brown pigmentation around the pupil spreads concentrically towards the periphery of the iris and the entire iris or parts become more brownish. Neither naevi nor freckles of the iris appear to be affected by the treatment. At 12 months, the incidence of iris hyperpigmentation with LUMIGAN 0,01 % eye drops, solution was 0,5 %. At 12 months, the incidence with bimatoprost 0,03 % eye drops, solution was 1,5 % (see section 4.8 Table 2) and did not increase following 3 years treatment.

In clinical studies, over 1800 patients have been treated with LUMIGAN 0,03 %. On combining the data from phase III monotherapy and adjunctive LUMIGAN 0,03 % usage, the most frequently reported adverse reactions were:

- Growth of eyelashes in up to 45 % in the first year with the incidence of new reports decreasing to 7 % at 2 years and 2 % at 3 years
- Conjunctival hyperaemia (mostly trace to mild and thought to be of a non-inflammatory nature) in up to 44 % in the first year with the incidence of new reports decreasing to 13 % at 2 years and 12 % at 3 years
- Ocular pruritus in up to 14 % of patients in the first year with the incidence of new reports decreasing to 3 % at 2 years and 0 % at 3 years. Less than 9 % of patients discontinued due to any adverse event in the first year with the incidence of additional patient discontinuations being 3 % at both 2 and 3 years.

Adverse reactions reported in phosphate containing eye drops
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.

Additional adverse events that have been seen with 0,03 % bimatoprost and may potentially occur also with LUMIGAN 0,01 % are presented in Table 2.

Table 2

System organ class	**Frequency**	**Adverse reaction**
Nervous system disorders	Common	Headache
	Uncommon	Dizziness
Eye disorders	Very common	Ocular pruritus, growth of eyelashes
	Common	Corneal erosion, ocular burning, allergic conjunctivitis, blepharitis, worsening of visual acuity, asthenopia, conjunctival oedema, foreign body sensation, ocular dryness, eye pain, photophobia, tearing, eye discharge, visual disturbance/blurred vision, increased iris pigmentation, eyelash darkening
	Uncommon	Retinal haemorrhage, uveitis, cystoid macular oedema, iritis, blepharospasm, eyelid retraction, periorbital erythema
Vascular disorders	Common	Hypertension
Skin and subcutaneous	Uncommon	Hirsutism

tissue disorders		
General disorders and administration site condition	Uncommon	Asthenia
Investigations	Common	Liver function test abnormal

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions via the national reporting system.

In case of a side effect, please contact MEAPV@abbvie.com

4.9 Overdose

No information is available on overdosage in humans. If overdosage occurs, treatment should be symptomatic and supportive. If LUMIGAN 0,01 % 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^2 is at least 210 times higher than the accidental dose of one bottle of LUMIGAN 0,01 % eye drops, solution in a 10 kg child.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Ophthalmologicals - antiglaucoma preparations and miotics - prostaglandin analogues - bimatoprost - ATC code: S01EE03

Mechanism of action

The mechanism of action by which bimatoprost reduces intraocular pressure in humans is 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.

Bimatoprost is a potent ocular hypotensive agent. It is a synthetic prostamide, structurally related to prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$), that does not act through any known prostaglandin receptors. Bimatoprost selectively mimics the effects of newly discovered biosynthesised substances called prostamides. The prostamide receptor, however, has not yet been structurally identified.

Clinical efficacy

During a 12-month pivotal study in adults with LUMIGAN 0,01 % eye drops, the mean diurnal IOP values measured at any visit over the 12-month study period differed by no more than 1.1 mmHg throughout the day and were never greater than 17.7 mmHg.

LUMIGAN 0,01 % eye drops contains BAK in a concentration of 200 ppm.

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

No clinically relevant effects on heart rate and blood pressure have been observed in clinical trials.

Paediatric population

The safety and efficacy of LUMIGAN in children aged 0 to less than 18 years has not been established.

5.2 Pharmacokinetic properties

Absorption

Bimatoprost penetrates the human cornea and sclera well *in vitro*. After ocular administration in adults, the systemic exposure of bimatoprost is very low with no accumulation over time. After once daily ocular administration of one drop of 0.3 mg/ml bimatoprost to both eyes 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 C_{max} and AUC $_{0\text{-}24hrs}$ values were similar on days 7 and 14 at approximately 0.08 ng/ml and 0.09 ng•hr/ml respectively, indicating that a steady bimatoprost concentration was reached during the first week of ocular dosing.

Distribution

Bimatoprost is moderately distributed into body tissues and the systemic volume of distribution in humans at steady-state was 0.67 l/kg. In human blood, bimatoprost resides mainly in the plasma. The plasma protein binding of bimatoprost is approximately 88 %.

Biotransformation

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

Bimatoprost is eliminated primarily by renal excretion, up to 67 % of an intravenous dose administered to healthy adult 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 was 1.5 l/hr/kg.

Characteristics in elderly patients

After twice daily dosing with bimatoprost 0.3 mg/ml eye drops, solution, the mean $AUC_{0\text{-}24hr}$ value of 0.0634 ng•hr/ml bimatoprost in the elderly (subjects 65 years or older) were significantly higher than 0.0218 ng•hr/ml in young healthy adults. However, this finding is not clinically relevant as systemic exposure for both 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.

5.3 Preclinical safety data

Effects in non-clinical studies were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.

Monkeys administered ocular bimatoprost concentrations of ≥0.3 mg/ml daily for 1 year had 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. The increased iris pigmentation appears to be caused by increased stimulation of melanin production in melanocytes and not by an increase in melanocyte number. No functional or microscopic changes related to the periocular effects have been observed, and the mechanism of action for the periocular changes is unknown.

Bimatoprost was not mutagenic or carcinogenic in a series of *in vitro* and *in vivo* studies.

Bimatoprost did not impair fertility in rats up to doses of 0.6 mg/kg/day (at least 103-times the intended human exposure). In embryo/foetal developmental studies abortion, but no developmental effects were seen in mice and rats at doses that were at least 860-times or 1700-times higher than the dose in humans, respectively. These doses resulted in systemic exposures of at least 33- or 97-times higher, respectively, than the intended human exposure. In rat peri/postnatal studies, maternal toxicity caused reduced gestation time, foetal death, and decreased pup body weights at ≥ 0.3 mg/kg/day (at least 41-times the intended human exposure). Neurobehavioural functions of offspring were not affected.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Benzalkonium chloride

Citric acid monohydrate

Dibasic sodium phosphate heptahydrate
Sodium chloride
Hydrochloric acid or sodium hydroxide (to adjust the pH)
Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.
Do not use more than 28 days after first opening.

6.4 Special precautions for storage

Store at or below 30°C. Keep bottle tightly closed when not in use. See section 6.3.

6.5 Nature and contents of container

LUMIGAN 0,01 % is supplied sterile in white opaque low density polyethylene bottles with a turquoise polystyrene screw cap. Each bottle contains 3 ml of solution and is packed into an outer carton.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

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