SCHEDULING STATUS

S4

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.

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 (25 %). Approximately 0,5 % 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.

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	Adverse reaction
Eye disorders	Corneal erosion, ocular burning, allergic conjunctivitis, blepharitis, worsening of visual acuity, visual disturbance, eyelash darkening, cataract, retinal haemorrhage, uveitis, cystoid macular oedema, iritis, blepharospasm, eyelid retraction, periorbital erythema
Skin and subcutaneous tissue disorders	Pigmentation of peri-ocular skin, hirsutism, abnormal hair growth
General disorders and administration site condition	Asthenia, peripheral oedema
Investigations	Liver function test (LFT) abnormal
Infections and infestations	Infection (primarily colds and upper respiratory tract infections)

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 to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification: A. 15.4 Ophthalmological preparations. Other

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

Bimatoprost reduces intraocular pressure (IOP) in humans 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 24 hours.

Limited experience is available with the use of bimatoprost in patients with open-angle glaucoma with pseudoexfoliative and pigmentary glaucoma, and chronic angle-closure glaucoma with patent iridotomy and no recommendation can be made.

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

5.2 Pharmacokinetic properties

Bimatoprost penetrates the human cornea and sclera well *in vitro.* After ocular administration, the systemic exposure of bimatoprost is very low with no accumulation over time.

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) in most subjects 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 drug concentration was reached during the first week of ocular dosing. Bimatoprost is moderately distributed into body tissues and the systemic volume of distribution in humans at steady-state was 0,67 l/kg.

As the concentration of the active substance for LUMIGAN 0,01 % has been reduced three-fold it is considered that the systemic medicine exposure will not increase compared with 0,03 % bimatoprost.

In human blood, bimatoprost resides mainly in the plasma. The plasma protein binding of bimatoprost is approximately 88 %.

Bimatoprost is not extensively metabolised in the human eye. Bimatoprost is the major circulating component 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.

Bimatoprost is eliminated primarily by renal excretion, up to 67 % of an **intravenous** dose 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 was 1,5 l/hr/kg.

Characteristics in elderly patients
After twice daily dosing with 0,03 % bimatoprost, 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.

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 30 days after first opening.

6.4 Special precautions for storage

Store at or below 25 °C. Keep bottle tightly closed when not in use. See section 6.3.

6.5 Nature and contents of container

2,5 ml filled in 5 ml; 5 ml and 7,5 ml filled in 10 ml white opaque low density polyethylene bottles with a turquoise polystyrene screw cap. Each bottle is packed into an outer carton.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

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8. REGISTRATION NUMBER

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