SCHEDULING STATUS
Schedule 4

PROPRIETARY NAME AND DOSAGE FORM
LUMIGAN® 0,03 % Eye drops

COMPOSITION
Each ml of sterile solution contains bimatoprost 0,3 mg.

Excipients:
Contains benzalkonium chloride 0,005 % m/v as a preservative

Sodium chloride
Sodium phosphate dibasic heptahydrate
Citric acid monohydrate
Purified water

PHARMACOLOGICAL CLASSIFICATION
A. 15.4 Ophthalmological preparations. Others

PHARMACOLOGICAL ACTION
Pharmacodynamic properties
Bimatoprost is an ocular hypotensive agent. It is a synthetic prostamide, structurally related to prostaglandin $F_{2\alpha}$, 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.

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.

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 patients

Elderly patients: After twice daily dosing, 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.

INDICATIONS

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

CONTRA-INDICATIONS

Hypersensitivity to bimatoprost or to any of the excipients.

WARNINGS AND SPECIAL PRECAUTIONS

LUMIGAN® 0,03 % should be used with caution in patients with active intraocular inflammation (e.g. uveitis) because the inflammation may be exacerbated.

Before treatment is initiated, patients should be informed of the possibility of eyelash growth since this has been observed during treatment with prostaglandin analogues, including LUMIGAN® 0,03 %.

Increased iris pigmentation has occurred when LUMIGAN® 0,03 % has been administered. Patients should be advised about the potential for increased brown iris pigmentation which 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 iridial pigmentation are not known. Iris colour changes seen with ophthalmic administration of LUMIGAN® 0,03 % may not be noticeable for several months to years. Neither nevi nor freckles of the iris appear to be affected by treatment.

LUMIGAN® 0,03 % has been reported to cause changes to pigmented tissues. When LUMIGAN® 0,03 % 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® 0,03 % solution comes repeatedly in contact with the skin surface. Thus, it is important to apply LUMIGAN® 0,03 % as instructed and to avoid it running onto the cheek or other skin areas.

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.

Macular oedema, including cystoid macular oedema, has been reported during treatment with LUMIGAN® 0,03 % for elevated IOP. LUMIGAN® 0,03 % 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® 0,03 % has not been studied in patients with inflammatory ocular conditions, neovascular, inflammatory, angle-closure glaucoma, congenital glaucoma or narrow-angle glaucoma.

LUMIGAN® 0,03 % 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 compromised respiratory function, no significant untoward respiratory effects have been seen.

LUMIGAN® 0,03 % has not been studied in patients with heart block more severe than first degree or uncontrolled congestive heart failure.

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® 0,03 % with other prostanglandin analogues should be monitored for changes to their intraocular pressure.

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

LUMIGAN® 0,03 % contains the preservative benzalkonium chloride, which may be absorbed by and cause discolouration of soft contact lenses. Patients wearing soft (hydrophilic) contact lenses should be instructed to remove contact lenses prior to administration of LUMIGAN® 0,03 % and wait at least 15 minutes following administration before reinserting soft contact lenses. LUMIGAN® 0,03 % should not be administered while wearing contact lenses.

Benzalkonium chloride, which is commonly used as a preservative in ophthalmic products, has been reported to cause punctate keratopathy and/or toxic ulcerative keratopathy. Since LUMIGAN® 0,03 % contains benzalkonium chloride, monitoring is required with frequent or prolonged use in dry eye patients or where the cornea is compromised.

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.

Effects on the 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.

INTERACTIONS
No interaction studies have been performed.

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

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

Concomitant use of LUMIGAN® 0,03 % and anti-glaucomatous 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 0,03 %) to be reduced in patients with glaucoma or ocular hypertension when used with other prostaglandin analogues (WARNINGS AND SPECIAL PRECAUTIONS).

PREGNANCY AND LACTATION
The safety of LUMIGAN® 0,03 % during pregnancy and lactation has not been established. LUMIGAN® 0,03 % should not be used during pregnancy unless clearly necessary.

It is not known whether LUMIGAN 0,03 % 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.

DOSAGE AND DIRECTIONS FOR USE
When used as monotherapy or as adjunctive therapy, the recommended dose is one drop of LUMIGAN® 0,03 % 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.

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.

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

Use in elderly
No dosage adjustment in elderly patients is necessary.

Use in children and adolescents (under the age of 18)
LUMIGAN® 0,03 % has only been studied in adults and therefore its use is not recommended in children or adolescents.

Use in hepatic and renal impairment
LUMIGAN® 0,03 % 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, LUMIGAN® 0,03 % had no adverse effect on liver function over 24 months.

SIDE EFFECTS
The most frequently reported treatment-related adverse events reported in clinical trials with LUMIGAN® 0,03 % 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, and 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.

The following undesirable effects definitely, probably or possibly related to treatment were reported during clinical trials with LUMIGAN® 0,03 %. Most were ocular, mild to moderate, and none was serious.

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).*

Eye disorders
Very common: Conjunctival/ocular hyperaemia, growth of eyelashes, eye pruritus
Common: Allergic conjunctivitis, asthenopia, blepharitis, blepharal pigmentation, cataract, conjunctival oedema, corneal erosion, eye discharge, eyelash discolouration (darkening), eye pain, eyelid erythema, eyelid pruritus, foreign body sensation in eyes, increased iris pigmentation, ocular burning, ocular dryness, eye irritation, photophobia, punctate keratitis, lacrimation increased, visual disturbance and worsening of visual acuity / blurred vision
Uncommon: Blepharospasm, iritis, retinal haemorrhage, uveitis

Skin and subcutaneous tissue disorders
Common: Skin hyperpigmentation

Uncommon: Hirsutism

General disorders and administration site conditions
Uncommon: Asthenia, peripheral oedema

Investigations
Common: Liver function test abnormal

Infections and infestations
Uncommon: Infection (primarily colds and upper respiratory tract infections)

Post-marketing experience
The following adverse reactions have been identified during post-marketing use of LUMIGAN 0,03 %. Because post-marketing reporting is voluntary and from a population of uncertain size, it is not possible to reliably estimate the frequency of these reactions:

Eye disorders
Periorbital and lid changes including deepening of the eyelid sulcus, erythema (periorbital), eyelid oedema, macular oedema, ocular discomfort

Skin and subcutaneous tissue disorders
Abnormal hair growth, skin discolouration

Gastrointestinal disorders
Nausea

Immune system disorders
Hypersensitivity reaction including signs and symptoms of eye allergy and allergic dermatitis

Nervous system disorders
Dizziness, headache

Respiratory, thoracic and mediastinal disorders
Asthma, exacerbation of asthma, dyspnoea

Vascular disorders
Hypertension

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT
No information is available on overdosage in humans. If overdosage occurs, treatment should

be symptomatic and supportive.

IDENTIFICATION
A clear colourless to slightly yellow solution with no foreign particles.

PRESENTATION
White opaque low density polyethylene bottles with a polystyrene screw cap, packed into an outer carton. Each bottle is filled with 3 ml solution.

STORAGE INSTRUCTIONS
Store at or below 25 °C.
Chemical and physical in-use stability has been demonstrated for 28 days at 25 °C.
From a microbiological point of view, the in-use storage time and conditions are the responsibility of the user.
Do not use more than 28 days after opening at 25 °C.
Keep bottle tightly closed when not in use.
KEEP OUT OF REACH AND SIGHT OF CHILDREN

REGISTRATION NUMBER
36/15.4/0157

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