SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Lumigan 0.3 mg/ml eye drops, solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One ml contains 0.3 mg bimatoprost.
For excipients, see 6.1.

3. PHARMACEUTICAL FORM

Eye drops, solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Reduction of elevated intraocular pressure in chronic open-angle glaucoma and ocular hypertension.

As monotherapy in patients:
- insufficiently responsive to first-line therapy
- intolerant or contra-indicated to first-line therapy

As adjunctive therapy to beta-blockers.

4.2 Posology and method of administration

The recommended dose is one drop 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.

If more than one topical ophthalmic medicinal product is being used, each one should be administered at least 5 minutes apart.

Use in children and adolescents (under the age of 18):
Lumigan has only been studied in adults and therefore its use is not recommended in children or adolescents.

Use in hepatic and renal impairment:
Lumigan has not been studied in patients with renal or hepatic impairment and should therefore be used with caution in such patients.

4.3 Contraindications

Hypersensitivity to bimatoprost or to any of the excipients.

4.4 Special warnings and special precautions for use

Before treatment is initiated, patients should be informed of the possibility of eyelash growth, darkening of the eyelid skin and increased iris pigmentation since these have been observed during treatment with Lumigan. Some of these changes may be permanent, and may lead to differences in appearance between the eyes when only one eye is treated. The change in iris pigmentation occurs slowly and may not be noticeable for several months.

Lumigan contains the preservative benzalkonium chloride, which may be absorbed by soft contact lenses. Contact lenses should be removed prior to instillation and may be reinserted 15 minutes following administration.

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 contains benzalkonium chloride, monitoring is required with frequent or prolonged use in dry eye patients or where the cornea is compromised.

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 heart block more severe than first degree or uncontrolled congestive heart failure.

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

Cystoid macular oedema has been uncommonly reported (>0.1% to <1%) following treatment with Lumigan and should therefore 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).

4.5 Interaction with other medicinal products and other forms of interaction

No interactions are anticipated in humans, since systemic concentrations of bimatoprost are extremely low (less than 0.2 ng/ml) following ocular dosing. Bimatoprost is biotransformed by any of multiple enzymes and pathways, and no effects on hepatic drug metabolising enzymes were observed in preclinical 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 interactions.

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

4.6 Pregnancy and lactation

Pregnancy
The safety of Lumigan has not been studied in pregnant women. Studies in rodents produced species-specific abortion at systemic exposure levels 33- to 97-times that achieved in humans after ocular administration. No drug related developmental effects were observed (see section 5.3). Lumigan should not be used during pregnancy unless clearly necessary.

Lactation
It is not known if bimatoprost is excreted in human milk, however, this substance is excreted in rat milk after intravenous administration. It is recommended that Lumigan is not used in nursing mothers.

4.7 Effects on ability to drive and use machines

Bimatoprost is not expected to affect 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.

4.8 Undesirable effects

In clinical studies, over 1800 patients have been treated with Lumigan. On combining the data from phase III monotherapy and adjunctive Lumigan usage, the most frequently reported treatment-related adverse events were: growth of eyelashes in up to 45%, conjunctival hyperaemia (mostly trace to mild) in up to 44%, and ocular pruritus in up to 14% of patients. Less than 9% 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 hyperaemia, growth of eyelashes, ocular pruritus.

Common (>1% to <10%): allergic conjunctivitis, asthenopia, blepharitis, cataract, 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 (>0.1% to <1%): blepharospasm, cystoid macular oedema, eyelid oedema, eyelid retraction, iritis, retinal haemorrhage, uveitis.

Systemic effects
Body as a whole
Common (>1% to <10%): headache
Uncommon (>0.1% to <1%): asthenia, infection (primarily colds and upper respiratory tract infections)

Gastrointestinal effects
Common (>1% to <10%): elevated liver function

Nervous system effects
Uncommon (>0.1% to <1%): dizziness

Cardiovascular
Common (>1% to <10%): hypertension

Metabolic
Uncommon (>0.1% to <1%): peripheral oedema

Skin
Uncommon (>0.1% to <1%): hirsutism

4.9 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 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 70-times higher than the accidental dose of one bottle of Lumigan in a 10 kg child.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: other antiglaucoma preparations;

ATC code: S 01 EX

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

During 12 months' monotherapy treatment, versus timolol, mean change from baseline in morning (08:00) intraocular pressure ranged from -7.9 to -8.8 mm Hg. At any visit, the mean diurnal IOP values measured over the 12-month study period differed by no more than 1.3 mmHg throughout the day and were never greater than 18.0 mmHg.

Compared to treatment with beta-blocker alone, adjunctive therapy with beta-blocker and bimatoprost lowered mean morning (08:00) intraocular pressure by -6.5 to -8.1 mmHg.

Limited experience is available with the use 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.

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 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 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 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.

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, 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

Monkeys administered ocular bimatoprost concentrations of ≥0.03% 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 cytogenic 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 (approximately 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
Sodium chloride
Sodium phosphate dibasic heptahydrate
Citric acid monohydrate
Hydrochloric acid or sodium hydroxide (to adjust pH)
Purified water

6.2 Incompatibilities

None known.

6.3 Shelf life

2 years.

4 weeks after first opening.

6.4 Special precautions for storage

No special precautions for storage.

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 times and conditions are the responsibility of the user and would normally not be longer than 28 days at 25°C.

6.5 Nature and contents of container

White opaque low density polyethylene bottles with polystyrene screw cap. Each bottle has a fill volume of 3 ml.

The following pack sizes are available: cartons containing 1 or 3 bottles of 3 ml. Not all pack sizes may be marketed.

6.6 Instructions for use and handling

None.

7. MARKETING AUTHORISATION HOLDER

Allergan Pharmaceuticals Ireland
Castlebar Road
Westport
Co. Mayo
Ireland

8. MARKETING AUTHORISATION NUMBER

EU/1/02/205/001-002

9. DATE OF FIRST AUTHORISATION

8 March 2002

10. DATE OF REVISION OF THE TEXT