LUMIGAN™ (bimatoprost ophthalmic solution) 0.03%

DESCRIPTION
Each mL contains: bimatoprost 0.3 mg with benzalkonium chloride 0.05 mg; sodium chloride; sodium phosphate, dibasic; citric acid; and purified water.

CLINICAL PHARMACOLOGY
Mechanism of Action:
Bimatoprost is a prostamide, a synthetic structural analog of prostaglandin with ocular hypotensive activity. It selectively mimics the effects of naturally occurring substances, prostamides. Bimatoprost is believed to lower intraocular pressure (IOP) in humans by increasing outflow of aqueous humor through both the trabecular meshwork and uveoscleral routes. Elevated IOP presents a major risk factor for glaucomatous field loss. The higher the level of IOP, the greater the likelihood of optic nerve damage and visual field loss.

Pharmacokinetics:
Absorption: After one drop of bimatoprost ophthalmic solution 0.03% was administered once daily to both eyes of 15 healthy subjects for two weeks, blood concentrations peaked within 10 minutes after dosing and were below the lower limit of detection (0.005 ng/mL) in most subjects within 1.5 hours after dosing. Mean Cmax and AUC values were similar on days 7 and 14 at approximately 0.06 ng/mL and 0.09 ng·hr/mL, respectively, indicating that steady state was reached during the first week of ocular dosing. There was no significant systemic drug accumulation over time.

Distribution: Bimatoprost is moderately distributed into body tissues with a steady-state volume of distribution of 0.67 L/kg. In human blood, bimatoprost resides mainly in the plasma. Approximately 12% of bimatoprost remains unbound in human plasma.

Metabolism: Bimatoprost is the major circulating species in the blood once it reaches the systemic circulation following ocular dosing. Bimatoprost then undergoes oxidation, N-dealkylation and glucuronidation to form a diverse variety of metabolites.

Elimination: Following an intravenous dose of radiolabeled bimatoprost (3.12 μg/kg) to six healthy subjects, the maximum blood concentration of unchanged drug was 12.2 ng/mL and decreased rapidly with an elimination half-life of approximately 45 minutes. The total blood clearance of bimatoprost was 1.5 L/hr/kg. Up to 67% of the administered dose was excreted in the urine while 25% of the dose was recovered in the feces.

Clinical Studies:
In clinical studies of patients with open angle glaucoma or ocular hypertension with a mean baseline IOP of 26 mmHg, the IOP-lowering effect of LUMIGAN™ once daily (in the evening) was 7.8 mmHg.

INDICATIONS AND USAGE
LUMIGAN™ is indicated for the reduction of elevated intraocular pressure in patients with open angle glaucoma or ocular hypertension who are intolerant of other intraocular pressure lowering medications or insufficiently responsive (failed to achieve target IOP determined after multiple measurements over time) to another intraocular pressure lowering medication.

CONTRAINDICATIONS
LUMIGAN™ is contraindicated in patients with hypersensitivity to bimatoprost or any other ingredient in this product.

WARNINGS
LUMIGAN™ has been reported to cause changes to pigmented tissues. These reports include increased pigmentation and growth of eyelashes and increased pigmentation of the iris and periocular tissue (eyelid).

These changes may be permanent.

LUMIGAN™ may gradually change eye color, increasing the amount of brown pigment in the iris by increasing the number of melaninocytes (pigment granules) in melanocytes. The long-term effects on the melanocytes and the consequences of potential injury to the melanocytes and/or deposition of pigment granules to other areas of the eye are currently unknown. The change in iris color occurs slowly and may not be noticeable for several months to years. Patients should be informed of the possibility of iris color change.

Eyelid skin darkening has also been reported in association with the use of LUMIGAN™.

LUMIGAN™ may gradually change eyelashes; these changes include increased length, thickness, pigmentation and

LUMIGAN™ should not be administered while wearing contact lenses.
LUMIGAN™ solution has not been studied in patients with renal or hepatic impairment and should therefore be used with caution in such patients.

Information for Patients: Patients should be informed that LUMIGAN™ has been reported to cause increased growth and darkening of eyelashes and darkening of the skin around the eye in some patients. These changes may be permanent.

Some patients may slowly develop darkening of the iris, which may be permanent.

When only one eye is treated, patients should be informed of the potential for a cosmetic difference between the eyes in eyelash length, darkness or thickness, and/or color changes of the eyelid skin or iris.

Patients should be instructed to avoid allowing the tip of the dispensing container to contact the eye, surrounding structures, fingers, or any other surface in order to avoid contamination of the solution by common bacteria known to cause ocular infections. Serious damage to the eye and subsequent loss of vision may result from using contaminated solutions.

Patients should also be advised that if they develop an intercurrent ocular condition (e.g., trauma or infection) or have ocular surgery, they should immediately seek their physician's advice concerning the continued use of the multidose container.

Patients should be advised that if they develop any ocular reactions, particularly conjunctivitis and eyelid reactions, they should immediately seek their physician's advice.

Contact lenses should be removed prior to instillation of LUMIGAN™ and may be reinserted 15 minutes following its administration. Patients should be advised that LUMIGAN™ contains benzalkonium chloride, which may be absorbed by soft contact lenses.

If more than one topical ophthalmic drug is being used, the drugs should be administered at least five (5) minutes between applications.

Carcinogenesis, Mutagenesis, Impairment of fertility: Carcinogenicity studies were not performed with bimatoprost.

Bimatoprost was not mutagenic or clastogenic in the Ames test, in the mouse lymphoma test, or in the in vivo mouse micronucleus tests.

Bimatoprost did not impair fertility in male or female rats up to doses of 0.6 mg/kg/day (approximately 103 times the recommended human exposure based on blood AUC levels).

Pregnancy: Teratogenic effects: Pregnancy Category C. In embryofetal developmental studies in pregnant mice and rats, abortion was observed at oral doses of bimatoprost which, at least achieved 33 or 37 times, respectively, the intended human exposure based on blood AUC levels.

At doses 41 times the intended human exposure based on blood AUC levels, the gestation length was reduced in the dams, the incidence of dead fetuses, late resorptions, peri- and postnatal pup mortality was increased, and pup body weights were reduced.

There are no adequate and well-controlled studies of LUMIGAN™ administration in pregnant women. Because animal reproduction studies are not always predictive of human response, LUMIGAN™ should be administered during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing mothers: It is not known whether LUMIGAN™ is excreted in human milk, although in animal studies, bimatoprost has been shown to be excreted in breast milk. Because many drugs are excreted in human milk, caution should be exercised when LUMIGAN™ is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

Geriatric Use: No overall clinical differences in safety or effectiveness have been observed between elderly and other adult patients.

ADVERSE REACTIONS
In clinical trials, the most frequent events associated with the use of LUMIGAN™ occurring in approximately 15% to 45% of patients, in descending order of incidence, included conjunctival hyperemia, growth of eyelashes, and ocular pruritus. Approximately 3% of patients discontinued therapy due to conjunctival hyperemia.

Ocular adverse events occurring in approximately 3% to 10% of patients, in descending order of incidence, included ocular dryness, visual disturbance, ocular burning, foreign body sensation, eye pain, pigmentation of the perilimbal skin, blepharitis, xerosis, superficial punctate keratitis, eyelid erythema, ocular irritation, and eyelid darkening. The following ocular adverse events reported in approximately 1% to 3% of patients, in descending order of incidence, included: eye discharge, tearing, photophobia, allergic conjunctivitis, asthenopia, increases in iris pigmentation, and conjunctival edema. In less than 1% of patients, intraocular inflammation was reported as iritis.

Systemic adverse events reported in approximately 10% of patients were infections (primarily colds and upper respiratory tract infections). The following systemic adverse events reported in approximately 1% to 5% of patients, in descending order of incidence, included headaches, abnormal liver function tests, asthma and hirudism.

OVERDOSAGE
No information is available on overdosage in humans. If overdosage with LUMIGAN™ occurs, treatment should be symptomatic.

Supply: The normal course and effect of dosage range up to 120 mg is not known. In case of acute iatrogenic overdosage, and in the event of toxic symptoms, systemic intoxication should be treated in the usual manner and without special supportive measures.