

DESCRIPTION:

Each ml contains

- Brimonidine tartrate 2mg
- Benzalkonium chloride 0.05mg

CLINICAL PHARMACOLOGY:

ALPHAGAN™ is an alpha adrenergic receptor agonist with high degree of selectivity to alpha₂ receptors. It has a peak ocular hypotensive effect occurring at two hours post-dosing. Fluorophotometric studies in animals and humans suggest that brimonidine tartrate has a dual mechanism of action by reducing aqueous humor production and increasing uveoscleral outflow.

After ocular administration of a 0.2% solution, plasma concentrations peaked within 1 to 4 hours and declined with a systemic half-life of approximately 3 hours.

In humans, systemic metabolism of brimonidine is extensive. It is metabolized primarily by the liver. Urinary excretion is the major route of elimination of the drug and its metabolites. Approximately 87% of an orally-administered radioactive dose was eliminated within 120 hours, with 74% found in the urine.

Elevated IOP presents a major risk factor in glaucomatous field loss. The higher the level of IOP, the greater the likelihood of optic nerve damage and visual field loss. ALPHAGAN™ has the action of lowering intraocular pressure with minimal effect on cardio vascular and pulmonary parameters.

In comparative clinical studies with Timolol 0.5% lasting upto 1 year, the IOP Lowering effect of ALPHAGAN™ is approximately 4-6mm Hg compared with approximately 6mm Hg for Timolol.



Eight percent of subjects were discontinued from studies due to inadequately controlled intraocular pressure, which in 30% of these patients occurred during the first month of therapy. Approximately 20% were discontinued due to adverse experiences.

INDICATIONS AND USAGE:

ALPHAGAN™ is indicated for lowering intraocular pressure in patients with open-angle glaucoma or ocular hypertension. The IOP lowering effect of ALPHAGAN™ diminishes over time in some patients.

This loss of effect appears with a variable time of onset in each patient and should be closely monitored.

CONTRAINDICATIONS:

ALPHAGAN™ is contraindicated in patients with hypersensitivity to brimonidine tartrate or any component of this medication. It is also contraindicated in patients receiving monoamine oxidase (MAO) inhibitor therapy.

PRECAUTIONS:

General: ALPHAGAN™ had minimal effect on blood pressure of patients in clinical studies, caution should be exercised in treating patients with severe cardio-vascular disease.

ALPHAGAN™ has not been studied in patients with hepatic and renal impairment; caution should be used in treating such patients.

ALPHAGAN™ should be used with caution in patients with depression, cerebral and coronary insufficiency, Raynaud's phenomenon, orthostatic hypotension or thromboangitis obliterans.

During the studies there was a loss of effect in some patients. The IOP-lowering efficacy observed with ALPHAGAN™ during the first month of therapy may not always reflect the long term level of IOP reduction.

For those patients whose IOP is not adequately controlled with twice daily dosing, an additional drop of brimonidine in the afternoon can be added. Patients prescribed TOP-lowering medication should be routinely monitored for IOP.

Information for patients: The preservative in ALPHAGAN™, benzalkonium chloride, may be absorbed by soft contact lenses.

Patients wearing soft contact lenses should be instructed to wait at least 15 minutes after instilling ALPHAGAN™ to insert soft contact lenses.

As with other drugs in this class, ALPHAGAN™ may cause fatigue and/or drowsiness in some patients. Patients who engage in hazardous activities should be cautioned of the potential for a decrease in mental alertness.

Drug Interactions: Although specific drug interaction studies have not been conducted with ALPHAGAN™, the possibility of an additive or a potentiating effect with CNS depressants (alcohol, barbiturates, opiates, sedatives and anaesthetics) should be considered. ALPHAGAN™ did not have significant effect on pulse and blood pressures in clinical studies. However, since alpha-agonists as a class, may reduce pulse or blood pressure, caution in using concomitant drugs such as beta blockers, (ophthalmic and systemic), antihypertensives and/or cardiac glycosides is advised.

Tricyclic antidepressants have been reported to blunt the hypotensive effects of systemic clonidine. It is not known whether the concurrent use of these agents with ALPHAGAN™ can lead to interference in IOP lowering effect. No data on the level of circulating catecholamines after ALPHAGAN™ is instilled are available. Caution, however, is advised in patients taking tricyclic anti-depressants which can affect the metabolism and update of circulating amines.

Carcinogenesis, mutagenesis, impairment of fertility :

No compound-related carcinogenic effects were observed in 21-month and 2-year studies in mice and rats given oral

doses of 2.5 mg/kg/day (as a free base) and 1.0 mg/kg/day, respectively (—77 and 118 times, respectively, the human plasma drug concentration following the recommended ophthalmic dose.)

ALPHAGAN™ was not mutagenic or cytogenic in a series of *in-vitro* and *in-viva* studies including the Ames test, host-mediated assay, chromosomal aberration assay in Chinese Hamster Ovary (CHO) cells, cytogenic studies in mice and dominant lethal assay.

Pregnancy: Reproduction studies performed in rats with oral doses of 0.66 mg base/kg revealed no evidence of impaired fertility or harmed foetus due to ALPHAGAN™. Dosing of this level produced 100 times the plasma drug concentration level seen in humans following multiple ophthalmic doses.

There are no studies of ALPHAGAN™ in pregnant women, however, in animal studies brimonidine crossed the placenta and entered into the foetal circulation to a limited extent. ALPHAGAN™ should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the foetus.

Nursing Mothers: It is not known whether ALPHAGAN™ is excreted in human milk, although in animal studies, brimonidine tartrate has been shown to be excreted in breast milk. A decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Paediatric use: Safety and effectiveness in paediatric patients have not been established.

ADVERSE REACTIONS:

Adverse events occurring in approximately 10 - 30% of the subjects, in descending order of incidence, included oral dryness, ocular hyperemia, burning and stinging, headache, blurring, foreign body sensation, fatigue/drowsiness, conjunctival follicles, ocular allergic reactions and ocular pruritis.

Events occurring in 3-9% of the subjects in descending order included corneal staining/erosion, photophobia, eyelid erythema, ocular ache/pain, ocular dryness, tearing, upper respiratory symptoms, eyelid edema, conjunctival edema, dizziness, blepharitis, ocular irritation, gastro intestinal symptoms, asthenia, conjunctival blanching, abnormal vision and muscular pain.

The following adverse reactions were reported in less than 3% of the patients: lid crusting, conjunctival hemorrhage, abnormal taste, insomnia, conjunctival discharge, depression, hypertension, anxiety, palpitations, nasal dryness and syncope.

OVERDOSAGE:

No information is available on overdose in humans. Treatment of an oral overdose includes supportive and symptomatic therapy, a patent airway should be maintained.

DOSAGE & ADMINISTRATION:

The recommended dose is one drop of ALPHAGAN™ in the affected eye(s) two times daily. For those patients whose **IOP** peaks in the afternoon or who need additional IOP control, an additional drop of brimonidine in the afternoon can be instilled.

HOW SUPPLIED:

ALPHAGAN™ ophthalmic solution is supplied as 0.2% Sterile Solution in 5ml white opaque plastic dropper bottles.

Note: Store in a cool place, protect from light. On prescription only

KEEP MEDICAMENT OUT OF THE REACH OF CHILDREN

WARNINGS:

NOT FOR INJECTION - Use the solution within one month after opening the container. Do not touch the nozzle tip to any surface since this may contaminate the solution. If irritation persists or increases discontinue use and consult physician.

DESCRIPTION

Each ml contains:

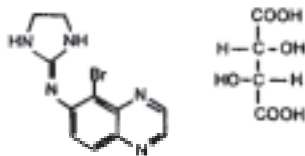
- Brimonidine tartrate 0.15% w/v
- Stabilized Oxylchloro complex (Purite) 0.005% w/v

ACTIONS:

ALPHAGAN® P (Brimonidine tartrate ophthalmic solution) 0.15% is a relatively selective alpha-2 adrenergic agonist for ophthalmic use. The chemical name of Brimonidine tartrate is 5-bromo-6- (2-imidazolidinylideneamino) quinoxaline L-tartrate. It is an off-white to pale yellow powder. It has a molecular weight of 442.24 as the tartrate salt, and is both soluble in water (1.5 mg/mL) and in the product vehicle (3.0 mg/mL) at pH 7.2.

The structural formula is:

Formula: $C_{11}H_{10}BrN_5 \cdot C_4H_6O_6$



In solution. ALPHAGAN® P (Brimonidine tartrate ophthalmic solution) 0.15% has a clear, greenish yellow colour. It has an osmolality of 250-350 mOsmol /Kg and a pH of 6.6-7.4

CLINICAL**PHARMACOLOGY:****Mechanism of action:**

ALPHAGAN® P is an alpha adrenergic receptor agonist. It has a peak ocular hypotensive effect occurring at two hours post-dosing. Fluorophotometric studies in animals and humans suggest that



Alphagan P
(brimonidine tartrate ophthalmic solution) 0.15%

Brimonidine tartrate has a dual mechanism of action by reducing aqueous humor production and increasing uveoscleral outflow. **Pharmacokinetics** : After ocular administration of either a 0.1% or 0.2% solution, plasma concentration peaked within 0.5 to 2.5 hours and declined with a systemic half-life, of approximately 2 hours. In humans, systemic metabolism of Brimonidine is extensive. It is metabolized primarily by the liver. Urinary excretion is the major route of elimination of the drug and its metabolites. Approximately 87% of an orally-administered radioactive dose was eliminated within 120 hours, with 74% found in the urine. **Clinical Evaluation:** Elevated IOP presents a major risk factor in glaucomatous field loss. The higher the level of IOP, the greater the likelihood of optic nerve damage and visual field loss. Brimonidine tartrate has the action of lowering intraocular pressure with minimal effect on cardiovascular and pulmonary parameters. Two clinical studies were conducted to evaluate the safety, efficacy, and acceptability of ALPHAGAN P (Brimonidine tartrate ophthalmic solution) 0.15% compared with ALPHAGAN administered three-times-daily in patients with open-angle glaucoma or ocular hypertension. Those results indicated that ALPHAGAN® P (Brimonidine tartrate ophthalmic solution) 0.15% is comparable in IOP lowering effect to ALPHAGAN P (Brimonidine tartrate ophthalmic solution) 0.2% and effectively lowers IOP in patients with open-angle glaucoma or ocular hypertension by approximately 2-5 mmHg.

INDICATIONS AND USAGE : ALPHAGAN® P is indicated for the lowering of intraocular pressure in patients with open-angle glaucoma or ocular hypertension.

CONTRAINDICATIONS : ALPHAGAN® P is contraindicated in patients with hypersensitivity to Brimonidine tartrate or any component of this medication. It is also contraindicated in patients receiving monoamine oxidase (MAO) Inhibitor therapy.

PRECAUTIONS: General: Although ALPHAGAN® P had

minimal effect on the blood pressure of patients in clinical studies caution should be exercised in treating patients with severe cardiovascular disease. ALPHAGAN® P has not been studied in patients with hepatic or renal impairment; caution should be used in treating such patients. ALPHAGAN® P should be used in caution in patients with depression, cerebral or coronary insufficiency, Raynaudis phenomenon, orthostatic hypotension, or thromboangitis obliterans. Patients prescribed IOP-lowering medication should be routinely monitored for IOP Information for **Patients:** as with other drugs in this class, ALPHAGAN® P may cause fatigue and or drowsiness in some patients. Patients who engage in hazardous activities should be cautioned of the potential for a decrease in mental alertness. **Drug : Interactions:** Although specific drug in teraction studies have not been conducted with ALPHAGAN® P, the possibility of an additive or potentiating effect with CNS depressants (alcohol, barbiturates, opiates, sedatives, or anesthetics) should be considered. Alpha-agonists, as a class, may reduce pulse and blood pressure. Caution in using concomilani drugs such as beta-blockers (ophthalmic and systemic), antihypertensive and/or cardiac glycosides is advised. Tricyclic antidepressants have been reported to blunt the hypotensive effect of systemic clonidine. It is not known whether the concurrent use of these agents with ALPHAGAN® P in humans can lead to resulting interference with the IOP lowering effect. No data on the level of circulating catecholamines after ALPHAGAN® P administration are available. Caution, however, is advised in patients taking tricyclic antidepressants which can affect the metabolism and uptake of circulating amines. Carcinogenesis, **Mutagenesla, and Impairment of Fertility:** No compound-related carcinogenic effects were observed in either mice or rates following a 21 month and 24-month study, respectively. In these studies, dietary administration of Sri monidine taitrate at doses up 2.5 mg/kg/day in mice and 1.0 mg/kg/day in rats achieved 86 and 55 times respectively, Ihe plasma drug concentration estimated in humans treated with one drop of ALPHAGAN® P into both eyes 3 times per day. Brimonidine tartrate was not mutagenic or cytogenic in a series of in Vitro

and in vivo studies including the Ames test, chromosomal aberration assay in Chinese Hamster Ovary (CHO) cells, a host-mediated assay and cytogenic studies in mice, and dominant lethal assay. **Pregnancy** : Teratogenic effects: Pregnancy Category B. Reproductive studies performed in rats with oral doses of 0.66mg base/kg revealed no evidence of impaired fertility or harm to the fetus due to ALPHAGAN® P. Dosing at this level produced on exposure that is 189 times higher than the exposure seen in humans following multiple ophthalmic doses. There are no adequate and weliconrolled studies in pregnant women. In animal studies, Brimonidine crossed the placenta and entered into the fetal circulation to a limited extent. ALPHAGAN® P should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus. **Nursing Mothers**: It is not known whether this drug is excreted in human milk; although in animal studies Brimonidine tartrate was excreted in breast milk. A decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. Pediatric use Safety and effectiveness in pediatric patients have not been established. Agitation, apnea, bradycardia, convulsions, cyanosis, depression, dyspnea, emotional instability, hypotension. hypothermia. hypotonia, hypoventilation, irritability, lethargy, somnolence, and stupor have been reported **in** pediatric patients receiving Brimonidine tartrate 0.2%. **Geriatric Use**: No overall differences in safety or effectiveness have been observed between elderly and other adult patients.

ADVERSE REACTIONS: Adverse events occurring in approximately 10-20% of the subjects included: allergic conjunctivitis. conjunctival hyperemia, and eye pruritis. Adverse events occurring in approximately 5-9% of the subjects included; burning sensation, conjunctival folliculosis, hypertension, oral dryness, and visual disturbance. Events occurring in approximately 1-4% of subjects included: allergic reaction, asthenia, blepharitis, bronchitis, conjunctival edema, conjunctival hemorrhage, conjunctivitis, cough, dizziness,

dyspepsia, dyspnea, epiphora, eye discharge, eye dryness, eye irritation, eye pain, eyelid edema, eyelid erythema, flu syndrome, follicular conjunctivitis, foreign body sensation, headache pharyngitis, photophobia, rash, rhinitis, sinus infection, sinusitis, stinging, superficial punctate keratopathy, visual field defect, vitreous floaters, and worsened visual acuity. The following events were reported in less than 1% of subjects; corneal erosion, insomnia, nasal dryness, somnolence, and taste perversion.

OVERDOSAGE: No information is available on overdosage in humans. Treatment of an oral overdose includes supportive and symptomatic therapy; a patent airway should be maintained.

DOSAGE AND ADMINISTRATION: The recommended dose is one drop of ALPHAGAN® P (Brimonidine tartrate ophthalmic solution) 0.15% in the affected eye(s) three times daily, approximately 8 hours apart.

HOW SUPPLIED: ALPHAGAN®P (Brimonidine tartrate ophthalmic solution) 0.15% is available in a 5mL plastic dropper bottles.

MEDICINE: Keep out of reach of children.

DESCRIPTION:

Each ml contains

- Levobunolol Hydrochloride USP 5 mg
- Benzalkonium Chloride USP 0.04 mg

ACTIONS:

Levobunolol is a noncardioselective beta-adrenoceptor blocking agent, equipotent at both beta₁ and beta₂ receptors. Levobunolol is 60 times more potent than its dextro-isomer in its beta-blocking activities; yet equipotent in its potential for direct myocardial depression. Accordingly, the levo isomer Levobunolol, is used. Levobunolol does not have significant local anaesthetic (membrane-stabilising) or intrinsic sympathomimetic activity. BETAGAN™ has been shown to be as effective as Timolol in lowering intraocular pressure.

BETAGAN™ when instilled in the eye will lower elevated intraocular pressure as well as normal intraocular pressure, whether or not accompanied by glaucoma. Elevated intraocular pressure presents a major risk factor in pathogenesis of glaucomatous field loss. The higher the level of intraocular pressure, the greater the likelihood of optic nerve damage and visual field loss. The primary mechanism of the ocular hypotensive action of Levobunolol HCl in reducing IOP is most likely a decrease in aqueous humor production. BETAGAN™ reduces intraocular pressure with little or no effect on pupil size in contrast to the miosis which cholinergic agents are known to produce.

The blurred vision and night blindness often associated with miotics would not be expected with the use of BETAGAN™. Patients with cataracts avoid the inability to see around lenticular opacities caused by pupil constriction.



BETAGAN™
LIQUIFILM™ (Levobunolol 0.5%)
Sterile Ophthalmic Solution

The onset of action with one drop of BETAGAN™ can be detected within one hour after treatment, with maximum effect seen between 2 and 6 hours. A significant decrease can be maintained for up to 24 hours following a single dose.

INDICATIONS:

BETAGAN™ is indicated for the control of intraocular pressure in chronic open angle glaucoma and ocular hypertension.

CONTRAINDICATIONS:

BETAGAN™ is contraindicated in patients with severe chronic obstructive pulmonary disease, bronchospasm, including bronchia] asthma, and uncontrolled congestive heart failure. BETAGAN™ is also contraindicated in those individuals who are hypersensitive to drug.

WARNINGS:

As with other topically applied ophthalmic drugs. BETAGAN™ may be absorbed systemically. NOT FOR INJECTION. Use the solution within one month after opening the container Do not touch the nozzle tip to any surface since this may contaminate solution. If irritation persists or increases discontinue use and consult physician.

PRECAUTIONS:

General - BETAGAN™ should be used with caution in patients with known contraindications to systemic use of bera-adrenoceptor blocking agents. These include abnormally low heart rate and heart block more severe than first degree. Congestive heart failure should he adequately controlled before beginning therapy with BETAGAN™. In patients with a history of significant cardiac disease, pulse rates should be monitored.

BETAGAN™ should be used with caution in patients with known hypersensitivity to other beta-adrenoceptor blocking agents. Use with caution in patients with known diminished pulmonary function.

Drug Interactions - BETAGAN™ may have additive effects in patients taking systemic anti-hypertensive drugs. These possible additive effects may include hypotension, including orthostatic hypotension, bradycardia, dizziness and/or syncope. Conversely, systemic beta-adrenoceptor blocking agents may potentiate the ocular hypotensive effect of BETAGAN™.

Pregnancy - There are no adequate and well controlled studies in pregnant women. Levobunolol should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

Nursing Mothers - It is not known whether this drug is excreted in human milk. Systemic beta blockers and topical Timolol Maleate are known to be excreted in human milk. Because similar drugs are excreted in human milk, caution should be exercised when BETAGAN™ is administered to a nursing woman.

Paediatric Use - Safety and effectiveness in children have not been established.

ADVERSE REACTIONS:

Blepharoconjunctivitis, transient ocular burning, stinging and decrease in heart rate and blood pressure have been reported occasionally with the use of BETAGAN™. Urticaria has been reported rarely with the use of BETAGAN™.

The following adverse effects have been reported rarely and a definite relationship with the use of BETAGAN™ has not been established: change in heart rhythm, iridocyclitis, browache,

headache, elevated liver enzymes, eructation, transient ataxia, ketargy, dizziness and itching.

DOSAGE & ADMINISTRATION:

The usual dose is one drop in the affected eye(s) once or twice a day

HOW SUPPLIED:

BETAGAN™ is available as a sterile ophthalmic solution in 5 ml plastic dropper bottles.

Note: Store in a cool place. Protect from light. On prescription only.

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

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.

Absorption: After one drop of bimatoprost ophthalmic solution 0.03% was administered once daily to both eyes of healthy subjects for two weeks, blood concentrations peaked within 10 minutes after dosing and were below the lower limit of detection (0.025 ng/mL) in most subjects within 1.5 hours after dosing. Mean C_{max} and AUC_{0-24hr} values were similar on days 7 and 14 at approximately 0.08 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



Go lower with
LUMIGAN™
 (bimatoprost ophthalmic solution) 0.03%

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: Following an intravenous dose of radiolabeled bimatoprost (3.12 μ g/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. 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™ ophthalmic solution 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™ ophthalmic solution 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 periorbital 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 melanosomes (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™ ophthalmic solution.

LUMIGAN™ may gradually change eyelashes; these changes include increased length, thickness, pigmentation, and number of lashes. Patients who are expected to receive treatment in only one eye should be informed about the potential for increased brown pigmentation of the iris, periorbital tissue, and eyelashes in the treated eye and thus, heterochromia between the eyes. They should also be advised of the potential for a disparity between the eyes in length, thickness, and/or number of eyelashes.

PRECAUTIONS

General: 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 corneal disease or a disruption of the ocular epithelial surface (see Information for Patients).

Patients may slowly develop increased brown pigmentation of the iris. This change may not be noticeable for several months to years (see Warnings). Typically the brown pigmentation around the pupil is expected to spread concentrically towards the periphery in affected eyes, but the entire iris or parts of it may also become more brownish. Until more information about increased brown pigmentation is available, patients should be examined regularly and, depending on the clinical situation, treatment may be stopped if increased pigmentation ensues. The increase in brown iris pigment is not expected to progress further upon discontinuation of treatment, but the resultant color change

may be permanent. Neither nevi nor freckles of the iris are expected to be affected by treatment.

LUMIGAN™ ophthalmic solution should be used with caution in patients with active intraocular inflammation (e.g., uveitis).

Macular edema, including cystoid macular edema, has been reported during treatment with bimatoprost ophthalmic solution. LUMIGAN™ 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 edema.

LUMIGAN™ ophthalmic solution has not been evaluated for the treatment of angle closure, inflammatory or neovascular glaucoma. LUMIGAN™ should not be administered while wearing contact lenses.

LUMIGAN™ ophthalmic 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™ ophthalmic solution 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 embryo/fetal developmental studies in pregnant mice and rats, abortion was observed at oral doses of bimatoprost, which achieved at least 33 or 97 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, pre- 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 reproductive 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™ ophthalmic solution 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™ (bimatoprost ophthalmic solution) 0.03% 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 periorbital skin, blepharitis, cataract, superficial punctate keratitis, eyelid erythema, ocular irritation, and eyelash 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, asthenia and hirsutism.

OVERDOSAGE

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

In oral (by gavage) mouse and rat studies, doses up to 100 mg/kg/day did not produce any toxicity. This dose expressed as mg/in² is at least 70 times higher than the accidental dose of one bottle of LUMIGAN™ ophthalmic solution for a 10kg child,

DOSAGE AND ADMINISTRATION

The recommended dosage is one drop in the affected eye(s) once daily in the evening. The dosage of LUMIGAN™ should not exceed once daily since it has been shown that more frequent administration may decrease the intraocular pressure lowering effect.

Reduction of the intraocular pressure starts approximately 4 hours after the first administration with maximum effect reached within approximately 8 to 12 hours.

LUMIGAN™ may be used concomitantly with other topical ophthalmic drug products to lower intraocular pressure. If more than one topical ophthalmic drug is being used, the drugs should be administered at least five (5) minutes apart.

HOW SUPPLIED

LUMIGAN™ ophthalmic solution is supplied sterile in opaque white plastic dropper bottles in the following sizes: 3.0 mL, 5.0 mL, and 7.5 mL. Note: LUMIGAN™ should be stored in the original container at 15^o to 25^oC. On prescription only. Keep out of the reach of children.

INTRODUCTION:

Glucomol (Timolol Maleate) is a nonspecific beta blocker with no significant intrinsic sympathomimetic activity. Being water soluble and free from local anesthetic properties, the drug is suitable for topical administration.

MODE OF ACTION:

Timolol is reported to suppress the formation of aqueous humor and thereby reduce the intraocular pressure. Topical application of Timolol does not affect endothelial permeability.

INDICATIONS:

Glucomol (Timolol) is indicated in chronic open angle glaucoma, ocular hypertension, aphakic glaucoma, secondary glaucoma.

PRECAUTIONS:

Owing to systemic absorption, the side-effects associated with beta blockers are likely to occur. Caution should be exercised in patients with bronchial asthma, COPD or CHF.

ADVERSE EFFECTS:

Local irritation, photophobia, blurred vision and itching

DOSAGE:

1. Drop twice daily or as advised by the Ophthalmologist.
- When a patient is transferred from a single anti-glaucoma agent continue the drug in use and add a drop of 0.25% w/v & 0.5% w/v of Glucomol in each affected eye twice a day. On the following day, discontinue the formerly used drug completely and continue with Glucomol.



GLUCOMOL™
(Timolol Maleate 0.25% & 0.5%)

PHARMACEUTICAL PRECAUTIONS:

It is desirable that the contents should not be used for more than a month after opening the container. Do not touch the dropper tip or let it touch any surface since this may contaminate the solution. If irritation persists or increases, discontinue the use and consult the Doctor.

AVAILABILITY:

Glucomol is available in 5ml plastic dropper bottles containing ophthalmic solution of Timolol maleate 0.25% w/v & 0.5% w/v strengths.