

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
022184Orig1s000

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use LUMIGAN® 0.01% and 0.03% (bimatoprost ophthalmic solution) safely and effectively. See full prescribing information for LUMIGAN®.

LUMIGAN® 0.01% and 0.03% (bimatoprost ophthalmic solution)

Initial U.S. Approval: 2001

-----**INDICATIONS AND USAGE**-----

LUMIGAN® is a prostaglandin analog indicated for the reduction of elevated intraocular pressure in patients with open angle glaucoma or ocular hypertension. (1)

-----**DOSAGE AND ADMINISTRATION**-----

One drop in the affected eye(s) once daily in the evening. (2)

-----**DOSAGE FORMS AND STRENGTHS**-----

Solution containing 0.1 mg/mL bimatoprost (LUMIGAN® 0.01%) or containing 0.3 mg/mL bimatoprost (LUMIGAN® 0.03%). (3)

-----**WARNINGS AND PRECAUTIONS**-----

- Pigmentation.
Pigmentation of the iris, periorbital tissue (eyelid) and eyelashes can occur. Iris pigmentation is likely to be permanent (5.1).
- Eyelash Changes.
Gradual change to eyelashes including increased length, thickness and number of lashes. Usually reversible. (5.2)

-----**ADVERSE REACTIONS**-----

Most common adverse reaction (range 25% -45%) is conjunctival hyperemia. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Allergan at 800-433-8871 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

-----**USE IN SPECIFIC POPULATIONS**-----

Use in pediatric patients below the age of 16 years is not recommended because of potential safety concerns related to increased pigmentation following long-term chronic use. (8.4)

**See 17 for Patient Counseling Information
Revised: 3/2010**

**FULL PRESCRIBING INFORMATION:
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*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

LUMIGAN[®] 0.01% and 0.03% (bimatoprost ophthalmic solution) is indicated for the reduction of elevated intraocular pressure in patients with open angle glaucoma or ocular hypertension.

2 DOSAGE AND ADMINISTRATION

The recommended dosage is one drop in the affected eye(s) once daily in the evening.

LUMIGAN[®] 0.01% and 0.03% (bimatoprost ophthalmic solution) should not be administered more than once daily since it has been shown that more frequent administration of prostaglandin analogs 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.

3 DOSAGE FORMS AND STRENGTHS

Ophthalmic solution containing bimatoprost 0.1 mg/mL (**LUMIGAN**[®] 0.01%) or containing bimatoprost 0.3 mg/mL (**LUMIGAN**[®] 0.03%).

4 CONTRAINDICATIONS

None

5 WARNINGS AND PRECAUTIONS

5.1 Pigmentation

Bimatoprost ophthalmic solution has been reported to cause changes to pigmented tissues. The most frequently reported changes have been increased pigmentation of the iris, periorbital tissue (eyelid) and eyelashes. Pigmentation is expected to increase as long as bimatoprost is administered. The pigmentation change is due to increased melanin content in the melanocytes rather than to an increase in the number of melanocytes. After discontinuation of bimatoprost, pigmentation of the iris is likely to be permanent, while pigmentation of the periorbital tissue and eyelash changes have been reported to be reversible in some patients. Patients who receive treatment should be informed of the possibility of

increased pigmentation. The long term effects of increased pigmentation are not known.

Iris color change 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 of the iris become more brownish. Neither nevi nor freckles of the iris appear to be affected by treatment. While treatment with **LUMIGAN**[®] 0.01% and 0.03% (bimatoprost ophthalmic solution) can be continued in patients who develop noticeably increased iris pigmentation, these patients should be examined regularly. (see PATIENT COUNSELING INFORMATION, 17.1).

5.2 Eyelash Changes

LUMIGAN[®] 0.01% and 0.03% may gradually change eyelashes and vellus hair in the treated eye. These changes include increased length, thickness, and number of lashes. Eyelash changes are usually reversible upon discontinuation of treatment.

5.3 Intraocular Inflammation

LUMIGAN[®] 0.01% and 0.03% should be used with caution in patients with active intraocular inflammation (e.g., uveitis) because the inflammation may be exacerbated.

5.4 Macular Edema

Macular edema, including cystoid macular edema, has been reported during treatment with bimatoprost ophthalmic solution. **LUMIGAN**[®] 0.01% and 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 edema.

5.5 Angle-closure, Inflammatory or Neovascular Glaucoma

LUMIGAN[®] 0.01% and 0.03% has not been evaluated for the treatment of angle-closure, inflammatory or neovascular glaucoma.

5.6 Bacterial Keratitis

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 PATIENT COUNSELING INFORMATION, 17.3).

5.7 Use with Contact Lenses

Contact lenses should be removed prior to instillation of LUMIGAN® 0.01% and 0.03% and may be reinserted 15 minutes following its administration.

6 ADVERSE REACTIONS

6.1 Clinical Studies Experience

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

In clinical studies with bimatoprost ophthalmic solutions (0.01% or 0.03%) the most common adverse event was conjunctival hyperemia (range 25% – 45%). Approximately 0.5% to 3% of patients discontinued therapy due to conjunctival hyperemia with 0.01% or 0.03% bimatoprost ophthalmic solutions. Other common events (>10%) included growth of eyelashes, and ocular pruritus.

Additional ocular adverse events (reported in 1 to 10% of patients) with bimatoprost ophthalmic solutions included ocular dryness, visual disturbance, ocular burning, foreign body sensation, eye pain, pigmentation of the periocular skin, blepharitis, cataract, superficial punctate keratitis, eyelid erythema, ocular irritation, eyelash darkening, eye discharge, tearing, photophobia, allergic conjunctivitis, asthenopia, increases in iris pigmentation, conjunctival edema, conjunctival hemorrhage, and abnormal hair growth. Intraocular inflammation, reported as iritis was reported in less than 1% of patients.

Systemic adverse events reported in approximately 10% of patients with bimatoprost ophthalmic solutions were infections (primarily colds and upper respiratory tract infections). Other systemic adverse events (reported in 1 to 5% of patients) included headaches, abnormal liver function tests, and asthenia.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

Teratogenic effects: 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 maximum intended human exposure based on blood AUC levels.

At doses at least 41 times the maximum 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® 0.01% and 0.03% (bimatoprost ophthalmic solution) 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.

8.3 Nursing Mothers

It is not known whether LUMIGAN® 0.01% and 0.03% 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.

8.4 Pediatric Use

Use in pediatric patients below the age of 16 years is not recommended because of potential safety concerns related to increased pigmentation following long-term chronic use.

8.5 Geriatric Use

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

8.6 Hepatic Impairment

In patients with a history of liver disease or abnormal ALT, AST and/or bilirubin at baseline, bimatoprost 0.03% had no adverse effect on liver function over 48 months.

10 OVERDOSAGE

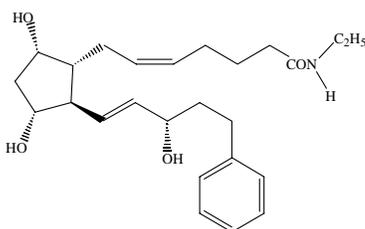
No information is available on overdosage in humans. If overdose with LUMIGAN® 0.01% and 0.03% (bimatoprost ophthalmic solution) occurs, treatment should be symptomatic.

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/m² is at least 70 times higher

than the accidental dose of one bottle of LUMIGAN® 0.03% for a 10 kg child.

11 DESCRIPTION

LUMIGAN® 0.01% and 0.03% (bimatoprost ophthalmic solution) is a synthetic prostamide analog with ocular hypotensive activity. Its chemical name is (Z)-7-[(1R,2R,3R,5S)-3,5-Dihydroxy-2-[(1E,3S)-3-hydroxy-5-phenyl-1-pentenyl]cyclopentyl]-5-N-ethylheptenamide, and its molecular weight is 415.58. Its molecular formula is C₂₅H₃₇NO₄. Its chemical structure is:



Bimatoprost is a powder, which is very soluble in ethyl alcohol and methyl alcohol and slightly soluble in water. LUMIGAN® 0.01% and 0.03% is a clear, isotonic, colorless, sterile ophthalmic solution with an osmolality of approximately 290 mOsmol/kg.

LUMIGAN® 0.01% contains **Active:** bimatoprost 0.1 mg/mL; **Preservative:** benzalkonium chloride 0.2 mg/mL; **Inactives:** sodium chloride; sodium phosphate, dibasic; citric acid; and purified water. Sodium hydroxide and/or hydrochloric acid may be added to adjust pH. The pH during its shelf life ranges from 6.8-7.8.

LUMIGAN® 0.03% contains **Active:** bimatoprost 0.3 mg/mL; **Preservative:** benzalkonium chloride 0.05 mg/mL; **Inactives:** sodium chloride; sodium phosphate, dibasic; citric acid; and purified water. Sodium hydroxide and/or hydrochloric acid may be added to adjust pH. The pH during its shelf life ranges from 6.8-7.8.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Bimatoprost, a prostaglandin analog, is 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.

12.3 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 (0.025 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 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 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.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Bimatoprost was not carcinogenic in either mice or rats when administered by oral gavage at doses of up to 2 mg/kg/day and 1 mg/kg/day respectively (at least 192 and 291 times the recommended human exposure based on blood AUC levels respectively) for 104 weeks.

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 (at least 103 times the recommended human exposure based on blood AUC levels).

14 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**[®] 0.03% (bimatoprost ophthalmic solution) once daily (in the evening) was 7-8 mmHg.

In a 3 month clinical study of patients with open angle glaucoma or ocular hypertension with an average baseline IOP of 23.5 mmHg, the IOP-lowering effect of **LUMIGAN**[®] 0.01% once daily (in the evening) was up to 7.5 mmHg and was approximately 0.5 mmHg less effective than **LUMIGAN**[®] 0.03%. In this same study, **LUMIGAN**[®] 0.01% also had a similar overall safety profile compared with **LUMIGAN**[®] 0.03%. After 12 months of treatment, discontinuations were 8.1% for **LUMIGAN**[®] 0.01% and 13.4% for **LUMIGAN**[®] 0.03%.

16 HOW SUPPLIED/STORAGE AND HANDLING

LUMIGAN[®] (bimatoprost ophthalmic solution) 0.01% is supplied sterile in opaque white low density polyethylene ophthalmic dispenser bottles and tips with turquoise polystyrene caps in the following sizes:

1 mL fill in a 5 mL container - NDC 0023-3205-01
2.5 mL fill in a 5 mL container - NDC 0023-3205-03
5 mL fill in a 10 mL container - NDC 0023-3205-05
7.5 mL fill in a 10 mL container - NDC 0023-3205-08

LUMIGAN[®] (bimatoprost ophthalmic solution) 0.03% is supplied sterile in opaque white low density polyethylene ophthalmic dispenser bottles and tips with turquoise polystyrene caps in the following sizes:

2.5 mL fill in 5 mL container - NDC 0023-9187-03
5 mL fill in 10 mL container - NDC 0023-9187-05
7.5 mL fill in 10 mL container - NDC 0023-9187-07

Storage: **LUMIGAN**[®] 0.01% and 0.03% should be stored at 2° to 25°C (36° to 77°F).

17 PATIENT COUNSELING INFORMATION

17.1 Potential for Pigmentation

Patients should be advised about the potential for increased brown pigmentation of the iris, which may be permanent. Patients should also be informed about the possibility of eyelid skin darkening, which may be reversible after discontinuation of **LUMIGAN**[®] 0.01% and 0.03% (bimatoprost ophthalmic solution).

17.2 Potential for Eyelash Changes

Patients should also be informed of the possibility of eyelash and vellus hair changes in the treated eye during treatment with **LUMIGAN**[®] 0.01% and 0.03%. These changes may result in a disparity between eyes in length, thickness, pigmentation, number of eyelashes or vellus hairs, and/or direction of eyelash growth. Eyelash changes are usually reversible upon discontinuation of treatment.

17.3 Handling the Container

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.

17.4 When to Seek Physician Advice

Patients should also be advised that if they develop an intercurrent ocular condition (e.g., trauma or infection), have ocular surgery, or develop any ocular reactions, particularly conjunctivitis and eyelid reactions, they should immediately seek their physician's advice concerning the continued use of **LUMIGAN**[®] 0.01% and 0.03%.

17.5 Use with Contact Lenses

Patients should be advised that **LUMIGAN**[®] 0.01% and 0.03% contains benzalkonium chloride, which may be absorbed by soft contact lenses. Contact lenses should be removed prior to instillation of **LUMIGAN**[®] and may be reinserted 15 minutes following its administration.

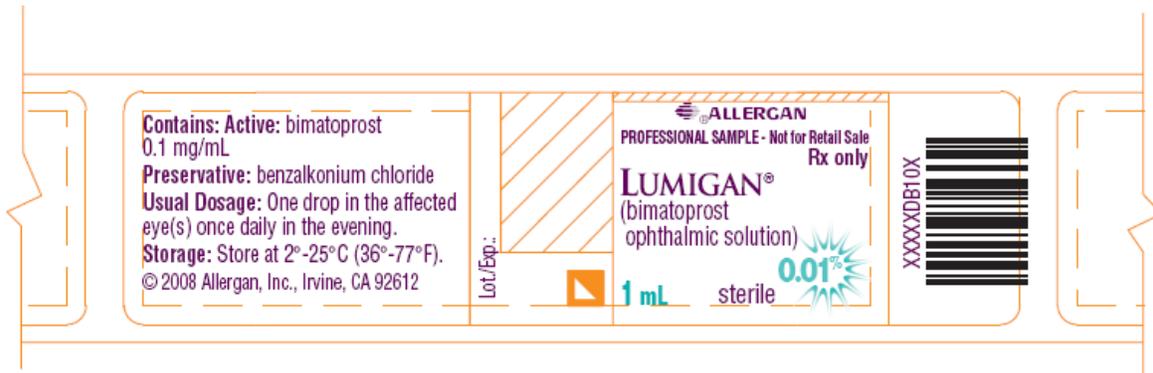
17.6 Use with Other Ophthalmic Drugs

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

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U.S. Patents 5,688,819 and 6,403,649



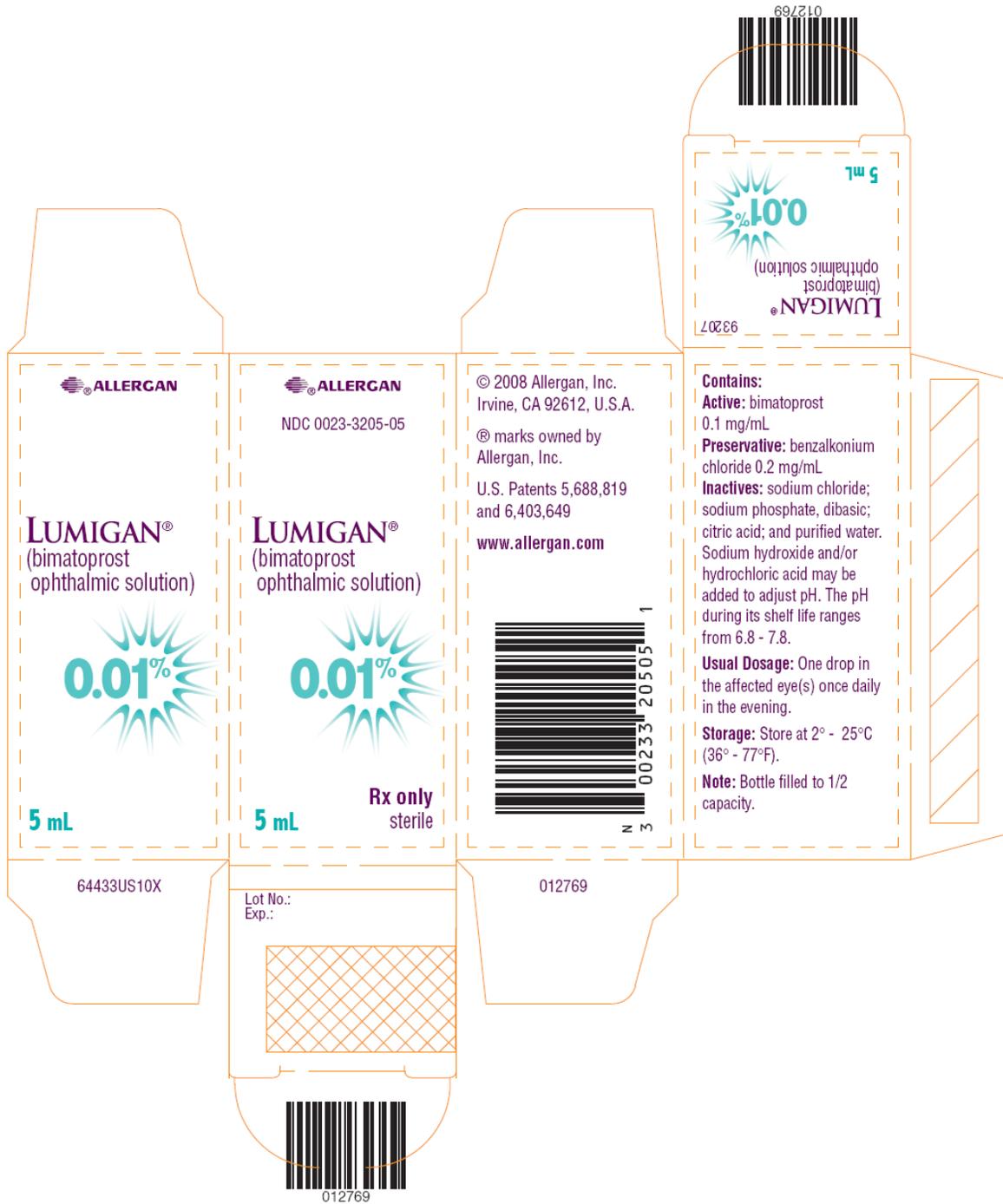






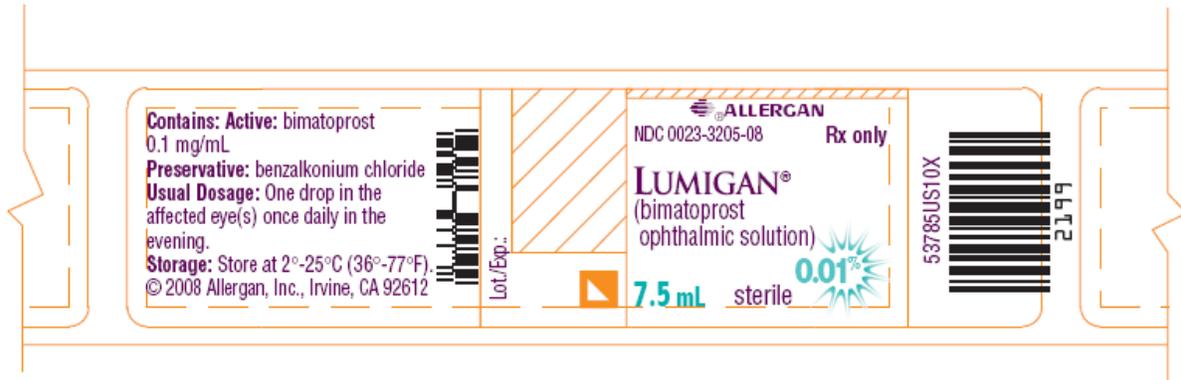












Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22184	ORIG-1	ALLERGAN INC	Lumigan (bimatoprost ophthalmic solution) 0.01%

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/s/

WILEY A CHAMBERS
08/31/2010