Welcome to the Third Edition of the Allergan Optometry Newsletter

Have You Visited allerganoptometry.com Lately?

Allergan is proud to offer LASTACAFT™ (alcaftadine ophthalmic solution) 0.25%.

If you're not already familiar with LASTACAFT™, please visit www.allerganoptometry.com to learn more.

Visit our optometry-dedicated website www.allerganoptometry.com for more information

Allergan is constantly updating its optometry website allerganoptometry.com, which was initially launched in February 2011.

Make sure you visit the site and register for updates, along with our e-newsletter. That way, you’ll always know the latest news from Allergan and what’s available to you at www.allerganoptometry.com.
Allergan supports Optometry’s Meeting®

Optometry’s Meeting® is coming up, and Allergan will be there hosting a variety of events including:

<table>
<thead>
<tr>
<th>Date</th>
<th>Time</th>
<th>Event</th>
<th>Topics &amp; Speakers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wed. June 15</td>
<td>12:00 PM-1:00 PM</td>
<td>OGS Allergan Promotional Lunch</td>
<td>LUMIGAN® CORE® Presentation, featuring Michael Chaglasian, OD Lunch will be served</td>
</tr>
<tr>
<td>Thurs. June 16</td>
<td>4:15 PM-4:45 PM</td>
<td>Discovery Theatre</td>
<td>LASTACAFT™, featuring Milton Hom, OD, FAAO</td>
</tr>
<tr>
<td>Fri. June 17</td>
<td>11:00 AM-12:00 PM</td>
<td>Discovery Theatre</td>
<td>RESTASIS®, featuring Mark Dunbar, OD, FAAO Lunch will be served</td>
</tr>
<tr>
<td>Fri. June 17</td>
<td>12:30 PM-1:00 PM</td>
<td>Discovery Theatre</td>
<td>LUMIGAN® 0.01%, featuring Murray Fingeret, OD</td>
</tr>
<tr>
<td>Fri. June 17</td>
<td>7:00 PM-9:00 PM</td>
<td>Allergan Promotional Dinner</td>
<td>LUMIGAN® 0.01%, featuring Ben Gaddie, OD, FAAO RESTASIS®, featuring Paul Karpecki, OD, FAAO LASTACAFT®, featuring Marc Bloomenstein, OD, FAAO</td>
</tr>
</tbody>
</table>

For more information about these programs or to register for these events, visit either www.optometristsmeeting.com or www.allergansupportsaoa.com.

We look forward to seeing you in Salt Lake City!

Optometrists Flood Allergan Events at SECO

This year at SECO, more than 300 ODs attended a symposium hosted by Allergan. The event was a success both in attendance and content. Information about RESTASIS® (Cyclosporine Ophthalmic Emulsion) 0.05% and LASTACAFT™ ophthalmic solution was shared and discussed. If you were at the meeting, thank you for coming and for sharing your thoughts. For those of you who were not able to make this year’s event, we look forward to seeing you at future events.
HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use LATISSE® safely and effectively. See full prescribing information for LATISSE®.

LATISSE® (bimatoprost ophthalmic solution) 0.03%
Initial U.S. Approval: 2001

INDICATIONS AND USAGE

LATISSE® is a prostaglandin analog, indicated to treat hypotrichosis of the eyelashes by increasing their growth including length, thickness and darkness. (1)

DOSAGE AND ADMINISTRATION

Apply nightly directly to the skin of the upper eyelid margin at the base of the eyelashes using the accompanying applicators. Blot any excess solution beyond the eyelid margin. Dispose of the applicator after one use. Repeat for the opposite eyelid margin using a new sterile applicator. (2)

DOSAGE FORMS AND STRENGTHS

Bimatoprost ophthalmic solution 0.3 mg/mL. (3)

WARNINGS AND PRECAUTIONS

Concurrent administration of LATISSE® and IOP-lowering prostaglandin analogs in ocular hypertensive patients may decrease the IOP-lowering effect. Patients using these products concomitantly should be closely monitored for changes to their intraocular pressure. (5.1)

Pigmentation of the eyelids and iris may occur. Iris pigmentation is likely to be permanent. (5.2, 5.3)

ADVERSE REACTIONS

Most common adverse events (incidence approximately 3% - 4%) are eye pruritus, conjunctival hyperemia, and skin hyperpigmentation. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Allergan at 1-800-433-8871 or the 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 and FDA-approved patient labeling

Revised: 09/2011
FULL PRESCRIBING INFORMATION

1 INDIICATIONS AND USAGE
LATISSE® (bimatoprost ophthalmic solution) 0.03% is indicated to treat hypotrichosis of the eyelashes by increasing their growth including length, thickness and darkness.

2 DOSAGE AND ADMINISTRATION
Ensure the face is clean, makeup and contact lenses are removed. Once nightly, place one drop of LATISSE® (bimatoprost ophthalmic solution) 0.03% on the disposable sterile applicator supplied with the package and apply evenly along the skin of the upper eyelid margin at the base of the eyelashes. The upper lid margin in the area of lash growth should feel lightly moist without runoff. Blot any excess solution runoff outside the upper eyelid margin with a tissue or other absorbent cloth. Dispose of the applicator after one use. Repeat for the opposite eyelid margin using a new sterile applicator.

Do not reuse applicators and do not use any other brush/applicator to apply LATISSE®.

Do not apply to the lower eyelash line (see WARNINGS AND PRECAUTIONS, 5.3, 5.4, and PATIENT COUNSELING INFORMATION, 17.1).

Additional applications of LATISSE® will not increase the growth of eyelashes.

Upon discontinuation of treatment, eyelash growth is expected to return to its pre-treatment level.

3 DOSAGE FORMS AND STRENGTHS
Bimatoprost ophthalmic solution 0.3 mg/mL.

4 CONTRAINDICATIONS
None

5 WARNINGS AND PRECAUTIONS

5.1 Effects on Intraocular Pressure
Bimatoprost ophthalmic solution (LUMIGAN®) lowers intraocular pressure (IOP) when instilled directly to the eye in patients with elevated IOP. In clinical trials, in patients with or without elevated IOP, LATISSE® lowered IOP, however, the magnitude of the reduction was not cause for clinical concern.

In ocular hypertension studies with LUMIGAN®, it has been shown that exposure of the eye to more than one dose of bimatoprost daily may decrease the intraocular pressure lowering effect. In patients using LUMIGAN® or other prostaglandin analogs for the treatment of elevated intraocular pressure, the concomitant use of LATISSE® may interfere with the desired reduction in IOP. Patients using prostaglandin analogs including LUMIGAN® for IOP reduction should only use LATISSE® after consulting with their physician and should be monitored for changes to their intraocular pressure (see PATIENT COUNSELING INFORMATION, 17.3).

5.2 Iris Pigmentation
Increased iris pigmentation has occurred when bimatoprost solution was administered. Patients should be advised about the potential for increased brown iris pigmentation which is likely to be permanent (see ADVERSE REACTIONS, 6.2 and PATIENT COUNSELING INFORMATION, 17.5).

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 pigmentation are not known. Iris color changes seen with administration of bimatoprost ophthalmic solution 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. Treatment with LATISSE® solution can be continued in patients who develop noticeably increased iris pigmentation.

5.3 Lid Pigmentation
Bimatoprost has been reported to cause pigment changes (darkening) to periorbital pigmented tissues and eyelashes. The pigmentation is expected to increase as long as bimatoprost is administered, but has been reported to be reversible upon discontinuation of bimatoprost in most patients (see PATIENT COUNSELING INFORMATION, 17.4).

5.4 Hair Growth Outside the Treatment Area
There is the potential for hair growth to occur in areas where LATISSE® solution comes in repeated contact with the skin surface. It is important to apply LATISSE® only to the skin of the upper eyelid margin at the base of the eyelashes using the accompanying sterile applicators, and to carefully blot any excess LATISSE® from the eyelid margin to avoid it running onto the cheek or other skin areas (see PATIENT COUNSELING INFORMATION, 17.6).

5.5 Intraocular Inflammation
LATISSE® solution should be used with caution in patients with active intraocular inflammation (e.g., uveitis) because the inflammation may be exacerbated.

5.6 Macular Edema
Macular edema, including cystoid macular edema, has been reported during treatment with bimatoprost ophthalmic solution (LUMIGAN®) for elevated IOP. LATISSE® 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.

5.7 Contamination of LATISSE® or Applicators
The LATISSE® bottle must be kept intact during use. It is important to use LATISSE® solution as instructed, by placing one drop on the single-use-per-eye applicator. The bottle tip should not be allowed to contact any other surface since it could become contaminated. The accompanying sterile applicators should only be used on one eye and then discarded since reuse of applicators increases the potential for contamination and infections. There have been reports of bacterial keratitis associated with the use of multiple-dose containers of topical ophthalmic products (see PATIENT COUNSELING INFORMATION, 17.2).

5.8 Use with Contact Lenses
LATISSE® contains benzalkonium chloride, which may be absorbed by soft contact lenses. Contact lenses should be removed prior to application of solution and may be reinserted 15 minutes following its administration (see PATIENT COUNSELING INFORMATION, 17.8).

6 ADVERSE REACTIONS
6.1 Clinical Studies Experience
The following information is based on clinical trial results from a multicenter, double-masked, randomized, vehicle-controlled, parallel study including 278 adult patients for four months of treatment.

The most frequently reported adverse events were eye pruritus, conjunctival hyperemia, skin hyperpigmentation, ocular irritation, dry eye symptoms, and erythema of the eyelid. These events occurred in less than 4% of patients.

Adverse reactions reported with bimatoprost ophthalmic solution (LUMIGAN®) for the reduction of intraocular pressure include, ocular dryness, visual disturbance, ocular burning, foreign body sensation, eye pain,
blepharitis, cataract, superficial punctate keratitis, eye discharge, tearing, photophobia, allergic conjunctivitis, asthenopia, increases in iris pigmentation, conjunctival edema, abnormal hair growth, iritis, infections (primarily colds and upper respiratory tract infections), headaches, and asthenia.

6.2 Postmarketing Experience
The following reactions have been identified during postmarketing use of LATISSE® in clinical practice. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. The reactions, which have been chosen for inclusion due to either their seriousness, frequency of reporting, possible causal connection to LATISSE®, or a combination of these factors, include: burning sensation (eyelid), erythema periorbital, eye swelling, eyelid irritation, eyelid edema, eyelids pruritus, iris hyperpigmentation, lacrimation increased, madarosis and trichorrhexis (temporary loss of a few eyelashes to loss of sections of eyelashes, and temporary eyelash breakage, respectively), periorbital and lid changes associated with a deepening of the eyelid sulcus, rash (including macular, erythematous, and pruritic limited to the eyelids and periorbital region), skin discoloration (periorbital), and vision blurred.

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 after topical ophthalmic administration to the cornea or conjunctival sac).

At doses at least 41 times the maximum intended human exposure, 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 bimatoprost ophthalmic solution 0.03% administration in pregnant women. Because animal reproductive studies are not always predictive of human response, LATISSE® 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 LATISSE® 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 LATISSE® is administered to a nursing woman.

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

8.5 Geriatric Use
No overall clinical differences in safety or effectiveness have been observed between elderly and other adult patients.
11 DESCRIPTION
**LATISSE®** (bimatoprost ophthalmic solution) 0.03% is a synthetic prostaglandin analog. Its chemical name is (Z)-7-[(1R,2R,3R,5S)-3,5-Dihydroxy-2-[(1E,3S)-3-hydroxy-5-phenyl-1-pentenyl]cyclopentyl]-N-ethyl-5-heptenamide, and its molecular weight is 415.58. Its molecular formula is C\textsubscript{25}H\textsubscript{37}NO\textsubscript{4}. Its chemical structure is:

![Chemical structure of bimatoprost]

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

**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 is a structural prostaglandin analog. Although the precise mechanism of action is unknown the growth of eyelashes is believed to occur by increasing the percent of hairs in, and the duration of the anagen or growth phase.

12.3 Pharmacokinetics

**Absorption**
After one drop of bimatoprost ophthalmic solution 0.03% was administered once daily into both eyes (cornea and/or conjunctival sac) 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\textsubscript{max} and AUC\textsubscript{0-24hr} values were similar on days 7 and 14 at approximately 0.08 ng/mL and 0.09 ng\cdot 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. 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 mcg/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 (approximately 192 and 291 times the recommended human exposure based on blood AUC levels after topical corneal and/or conjunctival sac administration 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.

14 CLINICAL STUDIES
LATISSE® solution was evaluated for its effect on overall eyelash prominence in a multicenter, double-masked, randomized, vehicle-controlled, parallel study including 278 adult patients for four months of treatment. The primary efficacy endpoint in this study was an increase in overall eyelash prominence as measured by at least a 1-grade increase on the 4-point Global Eyelash Assessment (GEA) scale, from baseline to the end of the treatment period (week 16). LATISSE® was more effective than vehicle as measured by the GEA score, with statistically significant differences seen at 8-week, 12-week, and 16-week (primary endpoint) treatment durations.

<table>
<thead>
<tr>
<th>Week</th>
<th>LATISSE® N=137</th>
<th>Vehicle N=141</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>7 (5%)</td>
<td>3 (2%)</td>
</tr>
<tr>
<td>4</td>
<td>20 (15%)</td>
<td>11 (8%)</td>
</tr>
<tr>
<td>8</td>
<td>69 (50%)</td>
<td>21 (15%)</td>
</tr>
<tr>
<td>12</td>
<td>95 (69%)</td>
<td>28 (20%)</td>
</tr>
<tr>
<td>16</td>
<td>107 (78%)</td>
<td>26 (18%)</td>
</tr>
<tr>
<td>20</td>
<td>103 (79%)</td>
<td>27 (21%)</td>
</tr>
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</table>

In this study, patients were also evaluated for the effect of LATISSE® solution on the length, thickness and darkness of their eyelashes. Improvements from baseline in eyelash growth as measured by digital image analysis assessing eyelash length, fullness/thickness, and darkness were statistically significantly more pronounced in the bimatoprost group at weeks 8, 12, and 16.
Table 2

<table>
<thead>
<tr>
<th>Efficacy endpoint at Week 16 (Mean Change from Baseline)</th>
<th>LATISSE®</th>
<th>Vehicle</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eyelash growth (length) (mm; % increase)</td>
<td>N=137 1.4; 25%</td>
<td>N=141 0.1; 2%</td>
</tr>
<tr>
<td>Fullness/thickness (mm²; % increase)</td>
<td>N=136 0.7; 106%</td>
<td>N=140 0.1; 12%</td>
</tr>
<tr>
<td>Eyelash darkness (intensity*; % increase in darkness)</td>
<td>N=135 -20.2; -18%</td>
<td>N=138 -3.6; -3%</td>
</tr>
</tbody>
</table>

* a negative value is representative of eyelash darkening

After the 16-week treatment period, a 4-week post-treatment period followed during which the effects of bimatoprost started to return toward baseline. The effect on eyelash growth is expected to abate following longer term discontinuation.

16 HOW SUPPLIED/STORAGE AND HANDLING

**LATISSE®** (bimatoprost ophthalmic solution) 0.03% is supplied sterile in opaque white low density polyethylene dispenser bottles and tips with turquoise polystyrene caps accompanied by 60 sterile, disposable applicators:

3 mL in a 5 mL bottle NDC 0023-3616-03

Storage: **LATISSE®** should be stored at 2° to 25°C (36° to 77°F).

17 PATIENT COUNSELING INFORMATION

17.1 Nightly Application

Patients should be informed that **LATISSE®** (bimatoprost ophthalmic solution) should be applied every night using only the accompanying sterile applicators. They should start by ensuring their face is clean, all makeup is removed, and their contact lenses removed (if applicable). Then, carefully place one drop of **LATISSE®** solution on the disposable sterile applicator and brush cautiously along the skin of the upper eyelid margin at the base of the eyelashes. If any **LATISSE®** solution gets into the eye proper, it will not cause harm. The eye should not be rinsed.

Additional applications of **LATISSE®** will not increase the growth of eyelashes.

Patients should be informed not to apply to the lower eyelash line. Any excess solution outside the upper eyelid margin should be blotted with a tissue or other absorbent material.

The onset of effect is gradual but is not significant in the majority of patients until 2 months. Patients should be counseled that the effect is not permanent and can be expected to gradually return to the original level upon discontinuation of treatment with **LATISSE®**.
17.2 Handling the Bottle and Applicator
Patients should be instructed that the LATISSE® bottle must be maintained intact and to avoid allowing the tip of the bottle or applicator to contact surrounding structures, fingers, or any other unintended surface in order to avoid contamination of the bottle or applicator by common bacteria known to cause ocular infections. Patients should also be instructed to only use the applicator supplied with the product once and then discard since reuse could result in using a contaminated applicator. Serious infections may result from using contaminated solutions or applicators.

17.3 Potential for Intraocular Pressure Effects
LATISSE® may lower intraocular pressure although not to a level that will cause clinical harm.

In patients using LUMIGAN® or other prostaglandin analogs for the treatment of elevated intraocular pressure, the concomitant use of LATISSE® may interfere with the desired reduction in IOP. Patients using prostaglandin analogs for IOP reduction should only use LATISSE® after consulting with their physician.

17.4 Potential for Eyelid Skin Darkening
Patients should be informed about the possibility of eyelid skin darkening, which may be reversible after discontinuation of LATISSE®.

17.5 Potential for Iris Darkening
Patients should be advised about the potential for increased brown iris pigmentation which is likely to be permanent. Increased iris pigmentation has occurred when bimatoprost solution was administered.

17.6 Potential for Unexpected Hair Growth or Eyelash Changes
Patients should be informed of the possibility of hair growth occurring outside of the target treatment area if LATISSE® repeatedly touches the same area of skin outside the treatment area. They should also be informed of the possibility of disparity between eyes in length, thickness, pigmentation, number of eyelashes or vellus hairs, and/or direction of eyelash growth. Eyelash changes are likely reversible upon discontinuation of treatment.

17.7 When to Seek Physician Advice
Patients should be advised that if they develop a new ocular condition (e.g., trauma or infection), experience a sudden decrease in visual acuity, 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 LATISSE®. Patients on IOP-lowering medications should not use LATISSE® without prior consultation with their physician.

17.8 Use with Contact Lenses
Patients should be advised that LATISSE® solution contains benzalkonium chloride, which may be absorbed by soft contact lenses. Contact lenses should be removed prior to application of LATISSE® and may be reinserted 15 minutes following its administration.

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17.9 FDA-approved Patient Labeling

PATIENT INFORMATION

LATISSE® (la teece) (bimatoprost ophthalmic solution) 0.03%
Read the Patient Information that comes with LATISSE® before you start using it and each time you get a refill. There may be new information. This leaflet does not take the place of talking with your physician about your treatment.

What is hypotrichosis of the eyelashes?

Hypotrichosis is another name for having inadequate or not enough eyelashes.

What is LATISSE® solution?

LATISSE® solution is a prescription treatment for hypotrichosis used to grow eyelashes, making them longer, thicker and darker.

Who should NOT take LATISSE®?

Do not use LATISSE® solution if you are allergic to one of its ingredients.

Are there any special warnings associated with LATISSE® use?

LATISSE® solution is intended for use on the skin of the upper eyelid margins at the base of the eyelashes. Refer to Illustration 2 below. DO NOT APPLY to the lower eyelid. If you are using LUMIGAN® or other products in the same class for elevated intraocular pressure (IOP), or if you have a history of abnormal IOP, you should only use LATISSE® under the close supervision of your physician.

LATISSE® use may cause darkening of the eyelid skin which may be reversible. LATISSE® use may also cause increased brown pigmentation of the colored part of the eye which is likely to be permanent.

It is possible for hair growth to occur in other areas of your skin that LATISSE® frequently touches. Any excess solution outside the upper eyelid margin should be blotted with a tissue or other absorbent material to reduce the chance of this from happening. It is also possible for a difference in eyelash length, thickness, fullness, pigmentation, number of eyelash hairs, and/or direction of eyelash growth to occur between eyes. These differences, should they occur, will usually go away if you stop using LATISSE®.

Who should I tell that I am using LATISSE®?

You should tell your physician you are using LATISSE® especially if you have a history of eye pressure problems.

You should also tell anyone conducting an eye pressure screening that you are using LATISSE®.

What should I do if I get LATISSE® in my eye?

LATISSE® solution is an ophthalmic drug product. LATISSE® is not expected to cause harm if it gets into the eye proper. Do not attempt to rinse your eye in this situation.

What are the possible side effects of LATISSE®?

The most common side effects after using LATISSE® solution are an itching sensation in the eyes and/or eye redness. This was reported in approximately 4% of patients. LATISSE® solution may cause other less common side effects which typically occur on the skin close to where LATISSE® is applied, or in the eyes. These include skin darkening, eye irritation, dryness of the eyes, and redness of the eyelids.
If you develop a new ocular condition (e.g., trauma or infection), experience a sudden decrease in visual acuity, have ocular surgery, or develop any ocular reactions, particularly conjunctivitis and eyelid reactions, you should immediately seek your physician’s advice concerning the continued use of LATISSE® solution.

**What happens if I stop using LATISSE®?**

If you stop using LATISSE®, your eyelashes are expected to return to their previous appearance over several weeks to months.

Any eyelid skin darkening is expected to reverse after several weeks to months.

Any darkening of the colored part of the eye known as the iris is NOT expected to reverse and is likely permanent.

**How do I use LATISSE®?**

LATISSE® solution is packaged as a 3 mL bottle of solution with 60 accompanying sterile, disposable applicators. The recommended dosage is one application nightly to the skin of the upper eyelid margin at the base of the eyelashes only.

Once nightly, start by ensuring your face is clean, makeup and contact lenses are removed. Remove an applicator from its tray. Then, holding the sterile applicator horizontally, place one drop of LATISSE® on the area of the applicator closest to the tip but not on the tip (see Illustration 1). Then immediately draw the applicator carefully across the skin of the upper eyelid margin at the base of the eyelashes (where the eyelashes meet the skin) going from the inner part of your lash line to the outer part (see Illustration 2). Blot any excess solution beyond the eyelid margin. Dispose of the applicator after one use.

Repeat for the opposite upper eyelid margin using a new sterile applicator. This helps minimize any potential for contamination from one eyelid to another.

**DO NOT APPLY** in your eye or to the lower lid. **ONLY** use the sterile applicators supplied with LATISSE® to apply the product. If you miss a dose, don’t try to “catch up.” Just apply LATISSE® solution the next evening. Fifty percent of patients treated with LATISSE® in a clinical study saw significant improvement by 2 months after starting treatment.
If any LATISSE® solution gets into the eye proper, it is not expected to cause harm. The eye should not be rinsed.

Don’t allow the tip of the bottle or applicator to contact surrounding structures, fingers, or any other unintended surface in order to avoid contamination by common bacteria known to cause infections.

Contact lenses should be removed prior to application of LATISSE® and may be reinserted 15 minutes following its administration.

Use of LATISSE® more than once a day will not increase the growth of eyelashes more than use once a day.

Store LATISSE® solution at 36° to 77°F (2° to 25°C).

**General Information about LATISSE®**

Prescription treatments are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not use LATISSE® solution for a condition for which it was not prescribed. Do not give LATISSE® to other people. It may not be appropriate for them to use.

This leaflet summarizes the most important information about LATISSE® solution. If you would like more information, talk with your physician. You can also call Allergan’s product information department at 1-800-433-8871.

**What are the ingredients in LATISSE®?**

**Active ingredient:** bimatoprost  
**Inactive ingredients:** benzalkonium chloride; 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.
In the 24-month oral (diet) rat study, conducted at 0.5, 2, and 8 mg/kg/day, pancreatic islet cell adenomas significantly exceeded the control rate in the low dose level. The hepatocellular carcinomas and pancreatic islet cell adenomas were not dose related. The low doses in mice and rats are approximately 1000 and 500 times greater, respectively, than the daily human dose of one drop (28 µL) of 0.05% RESTASIS® BID into each eye of a 60 kg person (0.001 mg/kg/day), assuming that the entire dose is absorbed.

Cyclosporine has not been found mutagenic/genotoxic in the Ames Test, the V79-HGPRT Test, the micronucleus test in mice and Chinese hamsters, the chromosome-aberration tests in Chinese hamster bone-marrow, the mouse dominant lethal assay, and the DNA-repair test in sperm from treated mice. A study analyzing sister chromatid exchange (SCE) induction by cyclosporine using human lymphocytes in vitro gave indication of a positive effect (i.e., induction of SCE).

No impairment in fertility was demonstrated in studies in male and female rats receiving oral doses of cyclosporine up to 15 mg/kg/day (approximately 15,000 times the human daily dose of 0.001 mg/kg/day) for 9 weeks (male) and 2 weeks (female) prior to mating.

Pregnancy-Teratogenic effects
Pregnancy category C.

Teratogenic Effects: No evidence of teratogenicity was observed in rats or rabbits receiving oral doses of cyclosporine up to 300 mg/kg/day during organogenesis. These doses in rats and rabbits are approximately 300,000 times greater than the daily human dose of one drop (28 µL) of 0.05% RESTASIS® BID into each eye of a 60 kg person (0.001 mg/kg/day), assuming that the entire dose is absorbed.

Non-Teratogenic Effects: Adverse effects were seen in reproduction studies in rats and rabbits only at dose levels toxic to dams. At toxic doses (rats at 30 mg/kg/day and rabbits at 100 mg/kg/day), cyclosporine oral solution, USP, was embryo- and fetotoxic as indicated by increased pre- and postnatal mortality and reduced fetal weight together with related skeletal retardations. These doses are 30,000 and 100,000 times greater, respectively, than the daily human dose of one-drop (28 µL) of 0.05% RESTASIS® BID into each eye of a 60 kg person (0.001 mg/kg/day), assuming that the entire dose is absorbed. No evidence of embryofetal toxicity was observed in rats or rabbits receiving cyclosporine oral doses up to 17 mg/kg/day or 30 mg/kg/day, respectively, during organogenesis. These doses in rats and rabbits are approximately 17,000 and 30,000 times greater, respectively, than the daily human dose.

Offspring of rats receiving a 45 mg/kg/day oral dose of cyclosporine from Day 15 of pregnancy until Day 21 post partum, a maternally toxic level, exhibited an increase in potential mortality; this dose is 45,000 times greater than the daily human topical dose, 0.001 mg/kg/day, assuming that the entire dose is absorbed. No adverse events were observed at oral doses up to 15 mg/kg/day (15,000 times greater than the daily human dose). There are no adequate and well-controlled studies of RESTASIS® in pregnant women.

RESTASIS® should be administered to a pregnant woman only if clearly needed.

Nursing Mothers
Cyclosporine is known to be excreted in human milk following systemic administration but not in human milk after topical treatment has not been investigated. Although blood concentrations are undetectable after topical administration of RESTASIS® ophthalmic emulsion, caution should be exercised when RESTASIS® ophthalmic emulsion is used in a patient who is breastfeeding.

Additional Nursing Considerations
In general, nursing mothers who receive cyclosporine ophthalmic emulsion should be advised to discard any drops that may have come in contact with the mother’s breast and nipple.

ADVERSE REACTIONS
The most common adverse event following the use of RESTASIS® was ocular burning (17%). Other events reported in 1% to 5% of patients included conjunctival hyperemia, discharge, epiphora, eye pain, foreign body sensation, pruritus, stinging, and visual disturbance (most often blurring).

DOSAGE AND ADMINISTRATION
Invert the unit dose vial a few times to obtain a uniform, white, opaque emulsion before using. Instill one drop of RESTASIS® ophthalmic emulsion twice a day in each eye approximately 12 hours apart. RESTASIS® can be used concomitantly with artificial tears, allowing a 15 minute interval between products. Discard vial immediately after use.

HOW SUPPLIED
RESTASIS® ophthalmic emulsion is packaged in single use vials. Each vial contains 0.4 mL filled in a 0.9 mL LDPE vial. 30 vials are packaged in a polypropylene tray with an aluminum peelable lid. The entire contents of this tray (30 vials) must be dispensed intact. RESTASIS® is also provided in a 60 count (2 x 30) package (one month supply) that must be dispensed intact.

30 Vials 0.4 mL each - NDC 0023-9163-30
60 (2 x 30) Vials 0.4 mL each - NDC 0023-9163-60


KEEP OUT OF THE REACH OF CHILDREN.
Rx Only

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Irvine, CA 92812, U.S.A.
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U.S. Patent 5,474,979
Made in the U.S.A.
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 1-800-433-8871 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: 08/2010
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 periorcular 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 \(C_{25}H_{37}NO_4\). 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<sub>max</sub> and AUC<sub>0-24hr</sub> 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:
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

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HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ZYMAXID® safely and effectively. See full prescribing information for ZYMAXID®.

ZYMAXID® (gatifloxacin ophthalmic solution) 0.5%
Initial U.S. Approval: 1999

INDICATIONS AND USAGE
ZYMAXID® ophthalmic solution is a topical fluoroquinolone anti-infective indicated for the treatment of bacterial conjunctivitis caused by susceptible strains of the following organisms:

- Haemophilus influenzae
- Staphylococcus aureus
- Staphylococcus epidermidis
- Streptococcus mitis group*
- Streptococcus oralis*
- Streptococcus pneumoniae

*Efficacy for this organism was studied in fewer than 10 infections.

DOSAGE AND ADMINISTRATION

Patients 1 year of age or older: Instill one drop every two hours in the affected eye(s) while awake, up to 8 times on Day 1. Instill one drop two to four times daily in the affected eye(s) while awake on Days 2 through 7. (1)

WARNINGs AND PRECAUTIONS

- Topical Ophthalmic Use Only
- Growth of Resistant Organisms with Prolonged Use
- Avoidance of Contact Lenses

ADVERSE REACTIONS

Most common adverse reactions occurring in ≥ 1% of patients included worsening of conjunctivitis, eye irritation, dysgeusia, and eye pain.

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

See 17 for PATIENT COUNSELING INFORMATION.

FULL PRESCRIBING INFORMATION: Contents*

1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
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   17.1 Avoiding Contamination of the Product
   17.2 Avoidance of Contact Lens Wear

*Sections or subsections omitted from the full prescribing information are not listed.

CONTRAINDICATIONS
None

Dosage Forms and Strengths

5 mL bottle filled with 2.5 mL of gatifloxacin ophthalmic solution, 0.5%. (3)

WARNINGS AND PRECAUTIONS

- Topical Ophthalmic Use Only
- Growth of Resistant Organisms with Prolonged Use
- Avoidance of Contact Lenses

Adverse reactions

Most common adverse reactions occurring in ≥ 1% of patients included worsening of conjunctivitis, eye irritation, dysgeusia, and eye pain.

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

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 05/2010

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE
ZYMAXID™ (gatifloxacin ophthalmic solution) 0.5% solution is indicated for the treatment of bacterial conjunctivitis caused by susceptible strains of the following organisms:

- Aerobic Gram-Positive Bacteria:
  - Staphylococcus aureus
  - Staphylococcus epidermidis
  - Streptococcus mitis group*
  - Streptococcus oralis*
  - Streptococcus pneumoniae

- Aerobic Gram-Negative Bacteria:
  - Haemophilus influenzae

*Efficacy for this organism was studied in fewer than 10 infections.

2 DOSAGE AND ADMINISTRATION

Patients 1 year of age or older: Instill one drop every two hours in the affected eye(s) while awake, up to 8 times on Day 1. Instill one drop two to four times daily in the affected eye(s) while awake on Days 2 through 7.

3 DOSAGE FORMS AND STRENGTHS

Five (5) mL bottle containing 2.5 mL of a 0.5% sterile topical ophthalmic solution.

4 CONTRAINDICATIONS

None

11 DESCRIPTION

CLINICAL PHARMACOLOGY

12.3 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

14 CLINICAL STUDIES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

17.1 Avoiding Contamination of the Product

17.2 Avoidance of Contact Lens Wear

*Sections or subsections omitted from the full prescribing information are not listed.
Additional adverse events reported with other formulations of gatifloxacin ophthalmic solution include chemosis, conjunctival hemorrhage, dry eye, eye discharge, eyelid edema, headache, increased lacrimation, keratitis, papillary conjunctivitis, and reduced visual acuity.

7 DRUG INTERACTIONS
Specific drug interaction studies have not been conducted with ZYMAXID™ ophthalmic solution.

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Pregnancy Category C
Teratogenic Effects: There were no teratogenic effects observed in rats or rabbits following oral gatifloxacin doses up to 50 mg/kg/day (approximately 1000-fold higher than the maximum recommended ophthalmic dose). However, skeletal/craniofacial malformations or delayed ossification, atrial enlargement, and reduced fetal weight were observed in fetuses from rats given ≥150 mg/kg/day (approximately 3000-fold higher than the maximum recommended ophthalmic dose). In a perinatal/postnatal study, increased late post-implantation loss and neonatal/perinatal mortalities were observed at 200 mg/kg/day (approximately 4000-fold higher than the maximum recommended ophthalmic dose).

Because there are no adequate and well-controlled studies in pregnant women, ZYMAXID™ solution should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

8.3 Nursing Mothers
Gatifloxacin is excreted in the breast milk of rats. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ZYMAXID™ is administered to a nursing woman.

8.4 Pediatric Use
The safety and effectiveness of ZYMAXID™ in infants below one year of age have not been established. ZYMAXID™ has been demonstrated in clinical trials to be safe and effective for the treatment of bacterial conjunctivitis in pediatric patients one year or older (see CLINICAL STUDIES, 14).

8.5 Geriatric Use
No overall differences in safety or effectiveness have been observed between elderly and younger patients.

11 DESCRIPTION
ZYMAXID™ sterile ophthalmic solution is an 8-methoxyfluoroquinolone anti-infective for the treatment of bacterial conjunctivitis. Its chemical name is (±)-1-Cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-(3-methyl-1-piperazinyl)-4-oxo-3-quinolincarboxylic acid sesquihydrate. Its molecular formula is C_{19}H_{23}FN_{4}O_{7}·1½H_{2}O, and its molecular weight is 402.42. Its chemical structure is:

![Chemical Structure of ZYMAXID™](image)

ZYMAXID™ is a clear, pale yellow, sterile, preserved aqueous solution with an osmolality of 260-330 mOsm/kg and a pH of 5.1-5.7.

ZYMAXID™ contains Active: gatifloxacin 0.5% (5 mg/mL); Inactives: benzalkonium chloride 0.005%; edetate disodium; purified water; and sodium chloride. May contain hydrochloric acid and/or sodium hydroxide to adjust pH.

12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
Gatifloxacin is a fluoroquinolone antibacterial (see CLINICAL PHARMACOLOGY, 12.4).

12.2 Pharmacokinetics
Gatifloxacin ophthalmic solution 0.3% or 0.5% was administered to one eye of 6 healthy male subjects each in an escalated dosing regimen starting with a single 2 drop dose, then 2 drops 4 times daily for 7 days, and finally 2 drops 8 times daily for 3 days. At all time points, serum gatifloxacin levels were below the lower limit of quantification (5 ng/mL) in all subjects.

12.4 Microbiology
Gatifloxacin is an 8-methoxyfluoroquinolone with a 3-methylpiperazinyl substituent at C7. The antibacterial action of gatifloxacin results from inhibition of DNA gyrase and topoisomerase IV. DNA gyrase is an essential enzyme that is involved in the replication, transcription, and repair of bacterial DNA. Topoisomerase IV is an enzyme known to play a key role in the partitioning of the chromosomal DNA during bacterial cell division. The mechanism of action of fluoroquinolones including gatifloxacin is different from that of aminoglycoside, macrolide, and tetracycline antibiotics. Therefore, gatifloxacin may be active against pathogens that are resistant to these antibiotics and these antibiotics may be active against pathogens that are resistant to gatifloxacin. There is no cross-resistance between gatifloxacin and the aforementioned classes of antibiotics. Cross resistance has been observed between systemic gatifloxacin and some other fluoroquinolones.

Resistance to gatifloxacin in vitro develops via multiple-step mutations. Resistance to gatifloxacin in vitro occurs at a general frequency of 1 x 10^{-10} to 1 x 10^{-14}.

Gatifloxacin has been shown to be active against most isolates of the following organisms both microbiologically and clinically, in conjunctival infections as described in the INDICATIONS AND USAGE, Section 1.

13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
There was no increase in neoplasms among B6C3F1 mice given gatifloxacin in the diet for 18 months at doses averaging 81 mg/kg/day in males and 90 mg/kg/day in females. These doses are approximately 1600-fold and 1850-fold higher, respectively, than the maximum recommended ophthalmic dose of 0.05 mg/kg/day in a 50 kg human.

There was no increase in neoplasms among Fischer 344 rats given gatifloxacin in the diet for 2 years at doses averaging 47 mg/kg/day in males and 139 mg/kg/day in females (900- and 2800-fold higher, respectively, than the maximum recommended ophthalmic dose). A statistically significant increase in the incidence of large granular lymphocyte (LGL) leukemia was seen in males treated with a high dose of approximately 2000-fold higher than the maximum recommended ophthalmic dose. Fischer 344 rats have a high spontaneous background rate of LGL leukemia and the incidence in high-dose males only slightly exceeded the historical control range established for this strain.

In genetic toxicity tests, gatifloxacin was positive in 1 of 5 strains used in bacterial reverse mutation assays: Salmonella strain TA102. Gatifloxacin was positive in vitro mammalian cell mutation and chromosome aberration assays. Gatifloxacin was positive in vitro unscheduled DNA synthesis in rat hepatocytes but not human leukocytes. Gatifloxacin was negative in vivo micronucleus tests in mice, cytogenetics test in rats, and DNA repair test in rats. The findings may be due to the inhibitory effects of high concentrations on eukaryotic type II DNA topoisomerase.

There were no adverse effects on fertility or reproduction in rats given gatifloxacin orally at doses up to 200 mg/kg/day (approximately 4000-fold higher than the maximum recommended ophthalmic dose for ZYMAXID™).

14 CLINICAL STUDIES
In two randomized, double-masked, multicenter clinical trials, where patients 1-89 years of age were dosed for 5 days, ZYMAXID™ solution was clinically superior to its vehicle on day 6 in patients with conjunctivitis and positive conjunctival cultures. Clinical outcomes for the trials demonstrated clinical success (resolution of conjunctival hyperemia and conjunctival discharge) of 58% (193/333) for the gatifloxacin-treated groups versus 45% (148/325) for the vehicle-treated groups. Microbiological outcomes for the same clinical trials demonstrated a statistically superior eradication rate for causative pathogens of 90% (301/333) for gatifloxacin vs. 70% (228/325) for vehicle. Please note that microbiological eradication does not always correlate with clinical outcome in anti-infective trials.

16 HOW SUPPLIED/STORAGE AND HANDLING
ZYMAXID™ (gatifloxacin ophthalmic solution) 0.5% is supplied sterile in a white, low density polyethylene (LDPE) bottle with a controlled dropper tip, and a tan, high impact polystyrene (HIPS) cap in the following sizes:

- 2.5 mL in 5 mL bottle: NDC 0023-3615-25


17 PATIENT COUNSELING INFORMATION
17.1 Avoiding Contamination of the Product
Patients should be instructed to avoid contaminating the applicator tip with material from the eye, fingers, or other source.

17.2 Avoidance of Contact Lens Wear
Patients should be advised not to wear contact lenses if they have signs and symptoms of bacterial conjunctivitis.
Absorption
Systemic absorption of timolol and timolol was assessed in healthy volunteers and patients following topical dosing with COMBIGAN®. Normal volunteers dosed with one drop of 160 mcg/mL (24.3 mg/mL) timolol and 1.25 mg/mL timolol concentrations of 50 mcg/mL and 240 mcg/mL, respectively. Plasma concentrations of timolol were determined by a sensitive specific assay. Plasma timolol concentrations were obtained approximately 1 to 3 hours post-dose. In a crossover study of COMBIGAN®, timolol was detected, but not timolol, in 10 of 15 treated subjects. The plasma concentration-time curve (AUC) for COMBIGAN® was 128 ± 65 mcg•h/mL, versus 141 ± 106 mcg•h/mL, for the respective monotherapies. Plasma concentrations of timolol and brimonidine were comparable following COMBIGAN® treatment versus monotherapy of timolol (14.9 ± 9.9 mcg/mL, versus 25.9 ± 12.2 mcg/mL, respectively; mean timolol of timolol was approximately 20% lower following monotherapy versus combination). In a parallel study in patients dosed twice daily with COMBIGAN®, twice daily with timolol 0.5%, or twice daily with placebo, one-hour post dose plasma concentrations of timolol and brimonidine were approximately 30-40% lower with COMBIGAN® than with timolol or placebo. The mean terminal half-life of timolol in COMBIGAN® appears to be due to twice daily dosing for COMBIGAN® compared to once daily dosing for timolol 0.2%.

Distribution
The protein binding of timolol is approximately 60%. The protein binding of brimonidine has not been studied.

Metabolism
In humans, brimonidine is extensively metabolized by the liver. Timolol is partially metabolized by the liver.

Excretion
In the crossover study in healthy volunteers, the plasma concentration of brimonidine declined with a systemic half-life of approximately 5 hours. The apparent systemic half-life of timolol was about 7 hours after ocular administration. Urinary excretion is the major route of elimination of brimonidine and its metabolites. Approximately 67% of an orally-administered radioactive dose of timolol was eliminated within 120 hours, with 74% in the urine. Unchanged timolol and its metabolites are excreted by the kidney.

Special Populations
COMBIGAN® has not been studied in patients with hepatic impairment. COMBIGAN® has not been studied in patients with renal impairment.

A study of patients with renal failure showed that timolol was not readily removed by dialysis. The effect of dialysis on brimonidine pharmacokinetics in patients with renal failure is not known.

Following oral administration of timolol maleate, the plasma half-life of timolol is essentially unchanged in patients with moderate renal insufficiency.

13 Nonclinical Toxicology
13.1 Carcinogenesis, Mutagenesis, and Impairment of Fertility
With brimonidine tartrate, no compound-related carcinogenic effects were observed in rats following 52-week oral gavage studies or 2-year inhalation studies, or following 26-week dermal studies. In rats, following 2-year oral dosing at 2 mg/kg/day timolol and 5 mg/kg/day timolol, no compound-related carcinogenic effects were observed. In mice and 1 mg/kg/day in rats achieved 150 and 210 times, respectively, the plasma Cmax of timolol. In brimonidine studies, dietary administration of brimonidine tartrate at doses up to 2.5 mg/kg/day in mice and 0.5 mg/kg/day in rats achieved 100 and 210 times, respectively, the plasma Cmax of brimonidine tartrate in humans treated with one drop of COMBIGAN® into both eyes twice daily, the recommended daily dosage.

In a two-year study of timolol maleate administered orally to rats, there was a statistically significantly increased incidence of adrenal cortical adenomas in male rats administered 300 mg/kg/day (approximately 25,000 times the maximum recommended human dose). The renal cortex and parathyroid medullary adenomas in female mice at 500 mg/kg/day, approximately 2,500 times the maximum recommended human dose. Similar differences were not observed in rats treated orally dosed equivalent to approximately 8,500 times the daily dosage of COMBIGAN® in humans.

In a lifetime oral study of timolol maleate in mice, there were statistically significant increases in the incidence of non-neoplastic and neoplastic tumors, luteoma uteri polyps and mammary adenocarcinomas in female mice at 500 mg/kg/day, approximately 20,000 times the maximum recommended human dose and 42,000 times the maximum recommended human dose, respectively, than those observed in female mice at 50 mg/kg/day. In a subsequent study in female mice, in which post-partum at 5 mg/kg, and in the absence of uterine and vaginal tumors, more importantly significant increase in the incidence of pulmonary tumors was observed at 300 mg/kg/day.

The increased occurrence of mammary adenocarcinomas was associated with elevations in serum prolactin levels; one occurred in female mice administered oral timolol at 50 mg/kg/day, but not at 5 or 50 mg/kg/day (approximately 420 to 4,200 times higher, respectively, than the MHD). In a subsequent study in female mice, in which post-partum at 5 mg/kg, and in the absence of uterine and vaginal tumors, a statistically significant increase in the incidence of pulmonary tumors was observed at 300 mg/kg/day.

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Brimonidine tartrate was not mutagenic or clastogenic in a series of in vivo and in vitro studies, including the Ames test, chromosomal aberration analysis assay, Chinese Hamster Ovary (CHO) cells, and three in vitro studies in CHO-mice; a hormone- mediated assay, cytogenetic study, and dominant lethal assay.

12.3 Pharmacokinetics
The maximum recommended human oral dosage, there were no clinically meaningful adult human female subjects who received oral dosages of up to 60 mg of timolol maleate for a period of up to 12 months. Post-mortem examinations were limited to the uterus and the lungs, a statistically

14 Clinical Studies
Clinical studies were conducted to compare the IOP-lowering effect over the course of the day of COMBIGAN® administered twice a day (BD) to individually-administered timolol tartrate opthalmic solution, 0.2% administered three times per day (TID) and timolol maleate ophthalmic solution, 0.5% BD in patients with glaucoma or ocular hypertension. COMBIGAN® BD provided an additional 1.6 to 3.6 mm Hg decrease in IOP compared to timolol TID and an additional 1.6 to 2.5 mm Hg decrease over timolol treatment in both studies. These treatment effects were sustained throughout the entire 24-hour period. The results of a 12-week, double-masked, placebo-controlled trial in patients with open angle glaucoma or ocular hypertension showed similar results. COMBIGAN® BD had a favorable safety profile versus concurrently administered timolol tad (0.2%) and timolol (0.5%) in the self-reported level of severity of sleepiness for patients age 40 or age.

11.5 Human Pharmacology
The plasma concentrations of timolol and brimonidine were approximately 30-40% lower with COMBIGAN® than with timolol or placebo. The mean terminal half-life of timolol in COMBIGAN® appears to be due to twice daily dosing for COMBIGAN® compared to once daily dosing for timolol 0.2%.

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5.6 Masking of thyrotoxicosis
Beta-adrenergic receptor blocking agents may mask certain clinical signs (e.g., tachycardia, hypertension). Patients suspected of developing thyrotoxicosis should be managed cautiously and beta-adrenergic blocking agents stopped immediately if thyrotoxicosis is suspected.

5.5 Contamination of topical ophthalmic products after use
There have been reports of bacterial contamination of topical ophthalmic solutions. There have been reports of bacterial contamination of topical ophthalmic solutions. These products should be examined for bacterial contamination before being used and should be discarded if any abnormalities are detected.

5.3 Bronchoconstriction
Some patients who are receiving beta-adrenergic blocking agents may experience bronchoconstriction. Adequate trials with systemic administration of beta-adrenergic blocking agents may occur with topical administration. Adequate trials with systemic administration of beta-adrenergic blocking agents may occur with topical administration.

OMS

2.2-3.12

5.1 Potentiation of respiratory reactions including asthma
COMBigan® is contraindicated in patients with bronchial asthma, a history of bronchial asthma, severe chronic obstructive pulmonary disease (see Warnings and Precautions). Brimonidine tartrate ophthalmic solutions are contraindicated in patients with a history of atopy or a history of severe hypersensitivity reaction to any component of this medication in the past. Local hypersensitivity reactions have occurred following the use of different components of these combinations (see Warnings and Precautions).

5.10 Impairment of beta-adrenergically mediated reflexes during surgery
In patients undergoing elective surgery, some authorities recommend that beta-adrenergic blocking agents be withheld up to 24 hours before surgery. Close observation of the patient is recommended when a beta blocker is administered to patients undergoing surgery. In patients taking beta-blocking agents, some authorities recommend that surgery include cardiovascular monitoring and anticholinergic medication (neostigmine, atropine or glycopyrronium bromide) (see Warnings and Precautions).

8.1 Pregnancy
Because of the potential for serious adverse reactions from brimonidine tartrate ophthalmic solutions, or a combination of these two components decreases elevated intraocular pressure, whether or not timolol maleate is also present. The safety and efficacy of the combination have been established in adults and children 2 years of age and older.

12.1 Mechanism of Action
COMBigan® is comprised of two components: timolol maleate and brimonidine tartrate. Timolol maleate is a beta-adrenergic blocking agent that competitively blocks the binding of epinephrine and other catecholamines to the beta-adrenergic receptors on the iris and ciliary muscle, resulting in a decrease in aqueous humor formation. Brimonidine tartrate is an alpha-2 adrenergic receptor agonist with a beta adrenergic receptor inhibitor indicated for the reduction of elevated intraocular pressure in patients with ocular hypertension or open-angle glaucoma. Repeated ophthalmic administration of timolol maleate results in a plasma concentration which is at least 100 times greater than that seen with the concomitant administration of 0.5% timolol maleate ophthalmic solution three times per day.

2 Dosage and Administration
The recommended dose is one drop of COMBigan® in the affected eye(s) twice daily or three times a day for 12-24 hours prior to surgery. It is not necessary to withhold this product to be used. This product protects the eye against desiccation, photophobia, and irritation during surgery.

3.3 Intranasal

10 Overdosage
COMBigan® is not available on overdose with COMBigan® in humans. There have been reports of inadvertent overdosage with timolol ophthalmic solution resulting in systemic symptoms such as hypotension. In these reports, there were no adverse symptoms associated with beta-adrenergic blocking agents such as flushing, headache, breathlessness, bradycardia, tachycardia, and cardiac arrest. Some evidence suggests that the risk of cardiac arrest is increased when brimonidine tartrate is not given as a beta-blocker for systemic hypertension.

5.9 Contamination of topical ophthalmic products after use
Because of the potential for serious adverse reactions from brimonidine tartrate ophthalmic solutions, or a combination of these two components decreases elevated intraocular pressure, whether or not timolol maleate is also present. The safety and efficacy of the combination have been established in adults and children 2 years of age and older.

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ACUVAIL®
(ketorolac tromethamine ophthalmic solution) 0.45%

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ACUVAIL® safely and effectively. See full prescribing information for ACUVAIL® ACUVAIL® (ketorolac tromethamine ophthalmic solution) 0.45%


INDICATIONS AND USAGE

ACUVAIL® ophthalmic solution is a nonsteroidal, anti-inflammatory indicated for the treatment of pain and inflammation following cataract surgery. (1)

DOSAGE AND ADMINISTRATION

One drop of ACUVAIL® should be applied by the patient to the affected eye twice daily beginning 1 day prior to cataract surgery, and continued through the first 2 weeks of the postoperative period. (2.1)

ADVERSE REACTIONS

Most common adverse reactions occurring in 1-6% of patients were increased intraocular pressure, conjunctival hemorrhage, and vision blurred. (6.1)

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

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 11/2009

FULL PRESCRIBING INFORMATION:

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1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
  2.1 Recommended Dosing
  2.2 Use with Other Topical Ophthalmic Medications
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS

5.1 Delayed Healing
5.2 Potential for Cross-Sensitivity
5.3 Increased Bleeding Time
5.4 Corneal Effects
5.5 Contact Lens Wear
6 ADVERSE REACTIONS

6.1 Clinical Studies
8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use

5 WARNINGS AND PRECAUTIONS

5.1 Delayed Healing

Topical nonsteroidal anti-inflammatory drugs (NSAIDs) may slow or delay healing. Topical corticosteroids are also known to slow or delay healing. Concomitant use of topical NSAIDs and topical steroids may increase the potential for healing problems.

5.2 Potential for Cross-Sensitivity

There is the potential for cross-sensitivity to acetylsalicylic acid, phenylacetic acid derivatives, and other NSAIDs. Therefore, caution should be used when treating individuals who have previously exhibited sensitivities to these drugs.

5.3 Increased Bleeding Time

With some NSAIDs, there exists the potential for increased bleeding time due to interference with thrombocyte aggregation. There have been reports that ocularly applied nonsteroidal anti-inflammatory drugs may cause increased bleeding of ocular tissues (including hyphemas) in conjunction with ocular surgery. It is recommended that ACUVAIL® ophthalmic solution be used with caution in patients with known bleeding tendencies or who are receiving other medications, which may prolong bleeding time.

5.4 Corneal Effects

Use of topical NSAIDs may result in keratitis. In some susceptible patients, continued use of topical NSAIDs may result in epithelial breakdown, corneal thinning, corneal erosion, corneal ulceration, or corneal perforation. These events may be sight threatening. Patients with evidence of corneal epithelial breakdown should immediately discontinue use of topical NSAIDs and should be closely monitored for corneal health.

DOSAGE FORMS AND STRENGTHS

• 4.5 mg/mL ketorolac tromethamine solution in a single-use vial. (3)

WARNINGS AND PRECAUTIONS

• Delayed healing (5.1)
• Potential for cross-sensitivity (5.2)
• Increased bleeding time due to interference with thrombocyte aggregation (5.3)
• Corneal effects including keratitis (5.4)

ADVERSE REACTIONS

Most common adverse reactions occurring in 1-6% of patients were increased intraocular pressure, conjunctival hemorrhage, and vision blurred. (6.1)
Postmarketing experience with topical NSAIDs suggests that patients with complicated ocular surgeries, corneal denervation, corneal epithelial defects, diabetes mellitus, ocular surface diseases (e.g., dry eye syndrome), rheumatoid arthritis, or repeat ocular surgeries within a short period of time may be at increased risk for corneal adverse events which may become sight threatening. Topical NSAIDs should be used with caution in these patients. Postmarketing experience with topical NSAIDs also suggests that use more than 1 day prior to surgery or use beyond 14 days post-surgery may increase patient risk for the occurrence and severity of corneal adverse events.

5.5 Contact Lens Wear
ACUVAIL® should not be administered while wearing contact lenses.

6 AVERSE REACTIONS
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 the rates in the clinical studies of another drug and may not reflect the rates observed in practice.

6.1 Clinical Studies
The most common adverse events were reported in 1-6% of patients and included increased intraocular pressure, conjunctival hyperemia and/or hemorrhage, corneal edema, ocular pain, headache, tearing and vision blurred. Some of these events may be the consequence of the cataract surgical procedure.

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Teratogenic Effects.

Pregnancy Category C: Ketorolac tromethamine, administered during organogenesis, was not teratogenic in rabbits and rats at oral doses of 3.6 mg/kg/day and 10 mg/kg/day, respectively. These doses are approximately 600 times and 1700 times higher respectively than the typical human topical ophthalmic daily dose of 0.35 mg (4.5 mg/mL x 0.04 mL/drop, BID) to an affected eye on a mg/kg basis. Additionally, when administered to rats after Day 17 of gestation at oral doses up to 1.5 mg/ kg/day (approximately 300 times the typical human topical ophthalmic daily dose), ketorolac tromethamine resulted in dystocia and increased pup mortality. There are no adequate and well-controlled studies in pregnant women. ACUVAIL® solution should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects: Because of the known effects of prostaglandin-inhibiting drugs on the fetal cardiovascular system (closure of the ductus arteriosus), the use of ACUVAIL® solution during late pregnancy should be avoided.

8.2 Nursing Mothers
Because many drugs are excreted in human milk, caution should be exercised when ACUVAIL® is administered to a nursing woman.

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

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

11 DESCRIPTION
ACUVAIL® (ketorolac tromethamine ophthalmic solution) 0.45% is a member of the pyrrolo-pyrrole group of nonsteroidal anti-inflammatory drugs (NSAIDs) for ophthalmic use. Its chemical name is (5S)-ketorolac tromethamine. Its chemical structure is:

\[
\text{C}_{23}\text{H}_{24}\text{Cl}_{2}\text{N}_{2}\text{O}_{11}\text{S}_{2}\text{P}_{2}\text{Cl}_{2}
\]

ACUVAIL® solution is supplied as a sterile isotonic aqueous 0.45% preservative-free solution, with a pH of approximately 6.8. ACUVAIL® solution is a racemic mixture of R(+) and S(-) ketorolac tromethamine. Ketorolac tromethamine may exist in three crystal forms. All forms are equally soluble in water. The pKa of ketorolac is 3.5. This white to off-white crystalline substance discolors on prolonged exposure to light. The osmolality of ACUVAIL® solution is approximately 285 mOsm/kg.

Contains: Active: ketorolac tromethamine 0.45%. Inactives: Carboxymethylcellulose; sodium chloride; sodium citrate dihydrate; and purified water with sodium hydroxide and/or hydrochloric acid to adjust pH.

12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
Ketorolac tromethamine is a nonsteroidal anti-inflammatory drug which, when administered systemically, has demonstrated analgesic, anti-inflammatory, and anti-pyretic activity. The mechanism of its action is thought to be due to its ability to inhibit prostaglandin biosynthesis.

12.3 Pharmacokinetics
The pharmacokinetics of ketorolac tromethamine ophthalmic solution 0.45% have not been assessed in humans.

Two drops of 0.5% ketorolac tromethamine ophthalmic solution instilled into the eyes of patients 12 hours and 1 hour prior to cataract extraction achieved a mean ketorolac concentration of 95 ng/mL in the aqueous humor of 8 of 9 eyes tested (range 40 to 170 ng/mL).

One drop of 0.5% ketorolac tromethamine ophthalmic solution was instilled into 1 eye and 1 drop of vehicle into the other eye TID in 26 normal subjects. Five (5) of 26 subjects had detectable concentrations of ketorolac in their plasma (range 11 to 22 ng/mL) at Day 10 during topical ocular treatment. The range of concentrations following TID dosing of 0.5% ketorolac tromethamine ophthalmic solution are approximately 4 to 6% of the steady state mean minimum plasma concentration observed following four times daily oral administration of 10 mg ketorolac in humans (0.29 ± 0.07 µg/mL).

13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
Ketorolac tromethamine was not carcinogenic in either rats given up to 5 mg/kg/day orally for 24 months or in mice given 2 mg/kg/day orally for 18 months. These doses are approximately 900 times and 300 times higher respectively than the typical human topical ophthalmic daily dose given as BID to an affected eye on a mg/kg basis.

Ketorolac tromethamine was not mutagenic in vitro in the Ames assay or in forward mutation assays. Similarly, it did not result in an in vivo increase in unscheduled DNA synthesis or an in vivo increase in chromosome breakage in mice. However, ketorolac tromethamine did result in an increased incidence in chromosomal aberrations in Chinese hamster ovary cells.

Ketorolac tromethamine did not impair fertility when administered orally to male and female rats at doses up to 9 mg/kg/day and 16 mg/kg/day, respectively. These doses are respectively 1500 and 2700 times higher than the typical human topical ophthalmic daily dose.

14 CLINICAL STUDIES
Two multicenter, randomized, double-masked, parallel group comparison studies including approximately 500 patients were conducted to evaluate the effects of ACUVAIL® on anterior chamber cell and flare, and ocular pain relief following cataract extraction with posterior chamber intraocular lens (IOL) implantation. Results of these studies indicated that patients receiving ACUVAIL® had a significantly higher incidence of clearing of anterior chamber inflammation 53% (167/318) vs. patients receiving vehicle 26% (41/155) at day 14.

ACUVAIL® was also significantly superior to vehicle in resolving ocular pain. On Day 1 post cataract surgery, 72% (233/322) of patients in the ACUVAIL® group were pain free compared to 40% (62/156) of patients in the vehicle group.

Results from clinical studies indicate that ketorolac tromethamine has no significant effect upon intraocular pressure; however, changes in intraocular pressure may occur following cataract surgery.

16 HOW SUPPLIED/STORAGE AND HANDLING
ACUVAIL® (ketorolac tromethamine ophthalmic solution) 0.45% is available as a sterile solution supplied in clear, LDPE, single-use vials packaged in 6 foil pouches, 5 vials per pouch:

30 Single-Use Vials 0.4 mL each: NDC 0023-3507-30

Storage: ACUVAIL® should be stored at 15° - 30°C (59° - 86°F). Store the vials in the pouch, protected from light. Fold pouch ends closed.

17 PATIENT COUNSELING INFORMATION
17.1 Slow or Delayed Healing
Patients should be informed of the possibility that slow or delayed healing may occur while using nonsteroidal anti-inflammatory drugs (NSAIDs).

17.2 Avoiding Contamination of the Product
Patients should be instructed that the solution from one individual single-use vial is to be used immediately after opening for administration to the affected eye. The remaining contents should be discarded immediately after administration. Avoid allowing the tip of the vial to contact the eye or surrounding structures because this could cause the tip to become contaminated by common bacteria known to cause ocular infections. Serious damage to the eye and subsequent loss of vision may result from using contaminated solutions.

Store the vials in the pouch, protected from light. Fold pouch ends closed.

17.3 Contact Lens Wear
ACUVAIL® solution should not be administered while wearing contact lenses.

17.4 Intercurrent Ocular Conditions
Patients should 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 ACUVAIL®.

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

Rx Only
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U.S. Patent Pending
Based on 72200511A
APC3TX10
(brimonidine tartrate ophthalmic solution) 0.1% and 0.15%

Sterile

DESCRIPTION

ALPHAGAN® P (brimonidine tartrate ophthalmic solution) 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 (0.6 mg/mL) and in the product vehicle (1.4 mg/mL) at pH 7.7. The structural formula is:

\[
\text{HN} \quad \text{NH} \quad \text{Br} \quad \text{N} \quad \text{C} \quad \text{O} \quad \text{H} \\
\text{H} \quad \text{C} \quad \text{O} \quad \text{H} \\
\text{HO} \quad \text{H} \\
\text{COOH}
\]

Formula: C₁₅H₁₁BrN₅ • C₆H₄O₆  CAS Number: 70359-46-5

In solution, ALPHAGAN® P (brimonidine tartrate ophthalmic solution) has a clear, greenish-yellow color. It has an osmolality of 250-350 mOsmol/kg and a pH of 7.4-8.0 (0.1%) or 6.6-7.4 (0.15%).

Each mL of ALPHAGAN® P contains:

Active ingredient: brimonidine tartrate 0.1% (1.0 mg/mL) or 0.15% (1.5 mg/mL).

Inactives: sodium carboxymethylcellulose; sodium borate; boric acid; sodium chloride; potassium chloride; calcium chloride; magnesium chloride; Purite® 0.005% (0.05mg/mL) as a preservative; purified water; with hydrochloric acid and/or sodium hydroxide to adjust pH.

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 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 concentrations 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 Evaluations:

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.

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® (brimonidine tartrate ophthalmic solution) 0.2%, and effectively lowers IOP in patients with open-angle glaucoma or ocular hypertension by approximately 2-6 mmHg.

A clinical study was conducted to evaluate the safety, efficacy, and acceptability of ALPHAGAN® P (brimonidine tartrate ophthalmic solution) 0.1% 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) 0.1% is equivalent in IOP lowering effect to ALPHAGAN® (brimonidine tartrate ophthalmic solution) 0.2%, and effectively lowers IOP in patients with open-angle glaucoma or ocular hypertension by approximately 2-6 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 brimonidine tartrate ophthalmic solution 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 with caution in patients with depression, cerebral or coronary insufficiency, Raynaud’s phenomenon, orthostatic hypotension, or thromboangiitis 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 interaction 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 concomitant drugs such as anti-hypertensives 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, Mutagenesis, and Impairment of Fertility:

No compound-related carcinogenic effects were observed in either mice or rats following a 21-month and 24-month study, respectively. In these studies, dietary administration of brimonidine tartrate at doses up to 2.5 mg/kg/day in mice and 1.0 mg/kg/day in rats achieved 150 and 120 times or 90 and 80 times, respectively, the plasma drug concentration (Cₘ₉) estimated in humans treated with one drop of ALPHAGAN® P 0.1% or 0.15% into both eyes 3 times per day.

Brimonidine tartrate was not mutagenic or cytogenic in a series of in vitro 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 and rabbits with oral doses of 0.66 mg base/kg revealed no evidence of impaired fertility or harm to the fetus due to ALPHAGAN® P. Dosing at this level produced an exposure in rats and rabbits that is 190 and 100 times or 120 and 60 times higher, respectively, than the exposure seen in humans following multiple ophthalmic doses of ALPHAGAN® P 0.1% or 0.15%.
There are no adequate and well-controlled 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:
In a well-controlled clinical study conducted in pediatric glaucoma patients (ages 2 to 7 years) the most commonly observed adverse events with brimonidine tartrate ophthalmic solution 0.2% dosed three times daily were somnolence (50%-83% in patients ages 2 to 6 years) and decreased alertness. In pediatric patients 7 years of age or older (>20kg), somnolence appears to occur less frequently (25%). Approximately 16% of patients on brimonidine tartrate ophthalmic solution discontinued from the study due to somnolence.
The safety and effectiveness of brimonidine tartrate ophthalmic solution have not been studied in pediatric patients below the age of 2 years. Brimonidine tartrate ophthalmic solution is not recommended for use in pediatric patients under the age of 2 years. (Also refer to Adverse Reactions section.)

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

Adverse reactions occurring in approximately 10-20% of the subjects receiving brimonidine ophthalmic solution (0.1-0.2%) included: allergic conjunctivitis, conjunctival hyperemia, and eye pruritus. Adverse events occurring in approximately 5-9% included: burning sensation, conjunctival folliculosis, hypertension, ocular allergic reaction, oral dryness, and visual disturbance.
Adverse events occurring in approximately 1-4% of the subjects receiving brimonidine ophthalmic solution (0.1-0.2%) included: allergic reaction, asthenia, blepharitis, blepharoconjunctivitis, blurred vision, bronchitis, cataract, conjunctival edema, conjunctival hemorrhage, conjunctivitis, cough, dizziness, dyspepsia, dyspnea, epiphora, eye discharge, eye dryness, eye irritation, eye pain, eyelid edema, eyelid erythema, fatigue, flu syndrome, follicular conjunctivitis, foreign body sensation, gastrointestinal disorder, headache, hypercholesterolemia, hypotension, infection (primarily colds and respiratory infections), insomnia, keratitis, lid disorder, pharyngitis, photophobia, rash, rhinitis, sinus infection, sinusitis, somnolence, stinging, superficial punctate keratopathy, tearing, visual field defect, vitreous detachment, vitreous disorder, vitreous floaters, and worsened visual acuity.
The following events were reported in less than 1% of subjects: corneal erosion, hordeolum, nasal dryness, and taste perversion.

The following events have been identified during post-marketing use of brimonidine tartrate ophthalmic solutions in clinical practice. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. The events, which have been chosen for inclusion due to either their seriousness, frequency of reporting, possible causal connection to brimonidine tartrate ophthalmic solutions, or a combination of these factors, include: bradycardia; depression; iritis; keratoconjunctivitis sicca; miosis; nausea; skin reactions (including erythema, eyelid pruritus, rash, and vasodilatation) and tachycardia. Apnea; bradycardia; hypotension; hypothermia; hypotonia; and somnolence have been reported in infants receiving brimonidine tartrate ophthalmic solutions.

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 in the affected eye(s) three times daily, approximately 8 hours apart.
ALPHAGAN® P ophthalmic solution may be used concomitantly with other topical ophthalmic drug products to lower intraocular pressure. If more than one topical ophthalmic product is being used, the products should be administered at least 5 minutes apart.

HOW SUPPLIED
ALPHAGAN® P is supplied sterile in opaque teal LDPE plastic bottles and droppers with purple high impact polystyrene (HIPS) caps as follows:

0.1% 0.15%

<table>
<thead>
<tr>
<th>Volume</th>
<th>Bottles</th>
<th>NDC Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 mL</td>
<td>10 mL</td>
<td>0023-9321-05</td>
</tr>
<tr>
<td>10 mL</td>
<td>10 mL</td>
<td>0023-9321-10</td>
</tr>
<tr>
<td>15 mL</td>
<td>15 mL</td>
<td>0023-9321-15</td>
</tr>
</tbody>
</table>

NOTE: Store at 15°-25° C (59-77°F).

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US Pat. 5,424,078; 5,736,165; 6,194,415; 6,248,741; 6,465,464; 6,562,873; 6,627,210; 6,641,834; 6,673,337
0.1%-9541X
0.15%-9174X
Based on 71816US10S
Re-order: 4960671

Alphagan P
Brimonidine Tartrate Ophthalmic Solution 0.1% & 0.15%
LASTACAFT®
(alcaftadine ophthalmic solution) 0.25%

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use LASTACAFT® safely and effectively. See full prescribing information for LASTACAFT®.
LASTACAFT® (alcaftadine ophthalmic solution) 0.25%
Initial U.S. Approval: 2010

INDICATIONS AND USAGE
LASTACAFT® is an H1 histamine receptor antagonist indicated for the prevention of itching associated with allergic conjunctivitis. (1)

DOSAGE AND ADMINISTRATION
Instill one drop in each eye once daily. (2)

DOSAGE FORMS AND STRENGTHS
Ophthalmic solution containing alcaftadine, 0.25% (2.5 mg/mL) (3)

WARNINGS AND PRECAUTIONS
- To minimize the risk of contamination, do not touch dropper tip to any surface. Keep bottle tightly closed when not in use. (5.1)
- LASTACAFT® should not be used to treat contact lens-related irritation. (5.2)
- Remove contact lenses prior to instillation of LASTACAFT®. (5.2)

ADVERSE REACTIONS
The most common ocular adverse reactions, occurring in < 4% of LASTACAFT® treated eyes, were eye irritation, burning and/or stinging on instillation, eye redness, and eye pruritus. (6.1)

The most common non-ocular adverse reactions, occurring in < 3% of subjects with LASTACAFT® treated eyes, were nasopharyngitis, headache and influenza. (6.2)

To report SUSPECTED ADVERSE REACTIONS, contact Allergan at 1-800-433-8871 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.
See 17 for PATIENT COUNSELING INFORMATION
Revised: 09/2011

FULL PRESCRIBING INFORMATION: CONTENTS*

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

1 INDICATIONS AND USAGE
LASTACAFT® is an H1 histamine receptor antagonist indicated for the prevention of itching associated with allergic conjunctivitis.

2 DOSAGE AND ADMINISTRATION
Instill one drop in each eye once daily.

3 DOSAGE FORMS AND STRENGTHS
Topical ophthalmic solution containing alcaftadine, 0.25% (2.5 mg/mL).

4 CONTRAINDICATIONS
None.

5 WARNINGS AND PRECAUTIONS
5.1 Contamination of Tip and Solution
To minimize contaminating the dropper tip and solution, care should be taken not to touch the eyelids or surrounding areas with the dropper tip of the bottle. Keep bottle tightly closed when not in use.

5.2 Contact Lens Use
Patients should be advised not to wear a contact lens if their eye is red.
LASTACAFT® should not be used to treat contact lens-related irritation.
LASTACAFT® should not be instilled while wearing contact lenses. Remove contact lenses prior to instillation of LASTACAFT®. The preservative in LASTACAFT®, benzalkonium chloride, may be absorbed by soft contact lenses. Lenses may be reinserted after 10 minutes following administration of LASTACAFT®.

5.3 Topical Ophthalmic Use Only
LASTACAFT® is for topical ophthalmic use only.

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

6.1 Ocular Adverse Reactions
The most frequent ocular adverse reactions, occurring in < 4% of LASTACAFT® treated eyes, were eye irritation, burning and/or stinging upon instillation, eye redness and eye pruritus.

6.2 Non-ocular Adverse Reactions
The most frequent non-ocular adverse reactions, occurring in < 3% of subjects with LASTACAFT® treated eyes, were nasopharyngitis, headache and influenza. Some of these events were similar to the underlying disease being studied.

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Pregnancy Category B. Reproduction studies performed in rats and rabbits revealed no evidence of impaired female reproduction or harm to the fetus due to alcaftadine. Oral doses in rats and rabbits of 20 and 80 mg/kg/day, respectively, produced plasma exposure levels approximately 200 and 9000 times the plasma exposure at the recommended human ocular dose. There are however, no adequate and well controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

8.3 Nursing Mothers
It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when LASTACAFT® is administered to a nursing woman.

8.4 Pediatric Use
Safety and effectiveness in pediatric patients below the age of 2 years have not been established.

8.5 Geriatric Use
No overall differences in safety or effectiveness were observed between elderly and younger subjects.

11 DESCRIPTION
LASTACAFT® is a sterile, topically administered H1 receptor antagonist containing alcaftadine for ophthalmic use.

12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
Alcaftadine is an H1 histamine receptor antagonist and inhibitor of the release of histamine from mast cells. Decreased chemotaxis and inhibition of eosinophil activation has also been demonstrated.

12.3 Pharmacokinetics
Absorption
Following bilateral topical ocular administration of alcaftadine ophthalmic solution, 0.25%, the mean plasma Cmax of alcaftadine was approximately 60 pg/mL and the median T1/2 occurred at 15 minutes. Plasma concentrations of alcaftadine were below the lower limit of quantification (10 pg/mL) by 3 hours after dosing. The mean Cmax of the active carboxylic acid metabolite was approximately 3 ng/mL and occurred at 1 hour after dosing. Plasma concentrations of the carboxylic acid metabolite were below the lower limit of quantification (100 pg/mL) by 12 hours after dosing. There was no indication of systemic accumulation or changes in plasma exposure of alcaftadine or the active metabolite following daily topical ocular administration.

Distribution
The protein binding of alcaftadine and its active metabolite are 39.2% and 62.7%, respectively.

Metabolism
The metabolism of alcaftadine is mediated by non-CYP450 cytosolic enzymes to the active carboxylic acid metabolite.

Excretion
The elimination half-life of the carboxylic acid metabolite is approximately 2 hours following topical ocular administration. Based on data following oral administration of alcaftadine, the carboxylic acid metabolite is primarily eliminated unchanged in the urine.

In vitro studies showed that neither alcaftadine nor the carboxylic acid metabolite substantially interacts with the 3A4 cytochrome P450 enzymes.

13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
Alcaftadine was not mutagenic or genotoxic in the Ames test, the mouse lymphoma assay or the mouse micronucleus assay.

14 CLINICAL STUDIES
Clinical studies were evaluated in conjunctival allergen challenge study (CAC) studies. LASTACAFT® was more effective than its vehicle in preventing ocular itching in patients with allergic conjunctivitis induced by an ocular allergen challenge, both at 3 minutes post-dosing and at 16 hours post-dosing of LASTACAFT®. The safety of LASTACAFT® was evaluated in a randomized clinical study of 909 subjects over a period of 6 weeks.

16 HOW SUPPLIED/STORAGE AND HANDLING
LASTACAFT® (alcaftadine ophthalmic solution) 0.25% is supplied in an opaque, white low-density polyethylene bottle with a white polypropylene cap. 3 mL fill in 5 mL bottle NDC 0023-4290-03

17 PATIENT COUNSELING INFORMATION
17.1 Sterility of Dropper Tip
Patients should be advised to not touch dropper tip to any surface, as this may contaminate the contents.

17.2 Concomitant Use of Contact Lenses
Patients should be advised not to wear a contact lens if their eye is red. Patients should be advised that LASTACAFT® should not be used to treat contact lens-related irritation. Patients should also be advised to remove contact lenses prior to instillation of LASTACAFT® in LASTACAFT®: benzalkonium chloride, may be absorbed by soft contact lenses. Lenses may be reinserted after 10 minutes following administration of LASTACAFT®

17.3 Topical Ophthalmic Use only
For topical ophthalmic administration only.

Structural Formula:
The drug product has a pH of approximately 7 and an osmolality of approximately 290 mOsm/kg.