Managing the Spectrum of Signs and Symptoms of Ocular Allergy

Insights from an optometrist and an immunologist, addressing treatment of all phases of the allergic response.

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Optometrists are the number one eyecare prescribers of ocular allergy drops in the United States, so I’m sure it comes as no surprise to most of us that 70% to 80% of people who have allergies report ocular symptoms. Although estimates vary widely, some researchers report that as many as 40% of the people in the United States are affected by allergic conjunctivitis. Today’s presentations focus on seasonal and perennial allergic conjunctivitis, which comprises 95% of all cases.

Value of Professional Care

Itching is the most common symptom of allergic conjunctivitis, and redness is the most common sign, but we may also see swelling, tearing or watery discharge, and we are likely to hear complaints of burning, stinging and foreign body sensation. Given the discomfort, it’s not surprising that people with ocular allergy want relief.

More than 41 million bottles of over-the-counter (OTC) and 4 million bottles of prescription anti-allergy ophthalmic medications are consumed annually, and a 2009 Gallup survey found that only 25% of patients who use eye drops for symptom relief use prescription eye drops. As these statistics suggest, many people try to alleviate their symptoms on their own. Ocular allergy sufferers often choose OTC eye drops that may exacerbate their symptoms. Vasoconstrictors, for example, provide temporary relief and can lead to rebound hyperemia with long-term use.

This underscores the importance of professional care to confirm a diagnosis of allergic conjunctivitis, which can be complicated by confounding factors and comorbidities. For instance, ocular itch is also a symptom of blepharitis, and researchers have found that people with dry eyes are prone to ocular allergies. In addition, the use of oral antihistamines can contribute to dry eye symptoms, which may complicate the diagnosis and treatment of allergic conjunctivitis.

Complex Problem

Given the complex nature of the allergic response, as well as the factors that can complicate diagnosis and treatment, medical professionals need therapies that can provide fast relief. In the articles that follow, Dr. Storms and I discuss the mechanisms and phases of the allergic response and how they lead us to appropriate treatment.

References on page 7
The Pathophysiology of Allergic Conjunctivitis

Differentiating the phases of the allergic response can guide your treatment choices.

The allergic response is a two-phase, globulin E-mediated hypersensitivity reaction. The early phase begins when an allergen triggers mast cell degranulation, causing the subsequent release of the preformed mediators histamine, tryptase, chymase and heparin. When the response manifests in the eyes, ocular itching, redness and chemosis occur within seconds of exposure and can last up to 40 minutes. The tryptase and histamine promote chemotaxis of basophils and eosinophils, which contribute to the late-phase response.11

The late phase usually begins 4 to 6 hours after initial exposure, leading to chemotaxis and the release of the newly formed mediators platelet-activating factor (PAF), leukotrienes, prostaglandins, cytokines and chemokines. Additional inflammatory cells, the neutrophils and eosinophils, are recruited into the conjunctiva 6 to 10 hours after exposure, with later infiltration of lymphocytes. This activity perpetuates the immune response up to 24 hours after exposure, causing itching, redness and chemosis to intensify.11

Understanding the phases of the immune response not only aids our diagnosis but helps us choose an appropriate treatment.

Calm the Itch

Numerous options exist for treating allergic conjunctivitis. These include allergen avoidance, which can be difficult for many people, use of artificial tears to wash away allergens, non-steroidal anti-inflammatory agents, mast cell stabilizers, antihistamines (often with mast cell stabilizing activity), and corticosteroids. When patients are in the acute phase of the allergic response — when itching is the chief complaint — I believe an excellent first-line choice is the dual-acting antihistamine-mast cell stabilizer bepotastine besilate ophthalmic solution 1.5% (Bepreve).

I choose bepotastine besilate ophthalmic solution 1.5% because it is a highly selective H1 receptor antagonist that inhibits eosinophil migration and activation but has no significant binding affinity for other receptors associated with sedation and dry eye, which are common side effects of some anti-allergy drugs.12-14 Bepotastine besilate ophthalmic solution 1.5% prevents the release of histamine from the mast cell, thereby inhibiting production of leukotrienes, PAF and interleukin-5.13 The efficacy and safety of bepotastine besilate ophthalmic solution 1.5% have been confirmed in clinical trials.

BEPREVE® (bepostatine besilate ophthalmic solution) 1.5% is a histamine H1 receptor antagonist indicated for the treatment of itching associated with signs and symptoms of allergic conjunctivitis.

Important Risk Information

BEPREVE® is contraindicated in patients with a history of hypersensitivity reactions to bepostatine or any of the other ingredients. BEPREVE® is for topical ophthalmic use only. To minimize risk of contamination, do not touch the dropper tip to any surface. Keep the bottle closed when not in use. BEPREVE® should not be used to treat contact lens-related irritation. Remove contact lenses prior to instillation of BEPREVE®.

The most common adverse reaction occurring in approximately 25% of patients was a mild taste following instillation. Other adverse reactions occurring in 2%-5% of patients were eye irritation, headache, and nasopharyngitis.

PLEASE SEE FULL PRESCRIBING INFORMATION FOR BEPREVE AND ALREX ON PAGES 8 AND 9.
Efficacy Established

Bepotastine besilate ophthalmic solution 1.5% was evaluated in two phase 3 clinical trials, using a conjunctival allergen challenge (CAC). In both trials, patients received bepotastine besilate ophthalmic solution 1.5% or placebo 15 minutes, 8 hours and 16 hours prior to CAC, and they assessed their ocular itching at 3, 5 and 7 minutes post CAC. Investigators evaluated conjunctival hyperemia at 7, 15 and 20 minutes post CAC, and they evaluated tolerability by adverse events, visual acuity, slit lamp biomicroscopy, intraocular pressure and dilated fundoscopy.

Within 15 minutes of the challenge, 77% and 88% of patients with severe itching responses (CAC grade ≥3, N = 17 and 23, respectively) to grasses and ragweed showed significant decreases in ocular itching when treated with bepotastine besilate ophthalmic solution 1.5% compared with placebo in a subanalysis of the entire study population. Another post hoc analysis of the two clinical trials showed that 68% of patients with severe itching responses reported no itching at 3 minutes when treated with bepotastine besilate ophthalmic solution 1.5% 15 minutes before allergen exposure (N=104 eyes), compared with 3% of patients who received placebo (N=98 eyes). Eyes treated with bepotastine besilate ophthalmic solution 1.5% had a rapid and clinically significant reduction (≥1U) of ocular itch within 15 minutes of administration. Among all patients, regardless of their itch severity, 95% of eyes treated with bepotastine besilate ophthalmic solution 1.5% had improvement within 15 minutes (N=156 eyes) compared with 47% of those receiving placebo.

Further analysis found that ocular itch relief was sustained for 8 hours after bepotastine besilate ophthalmic solution 1.5% was administered, and the drug reduced ocular itch by one or more units in 90% of treated eyes (N=156 eyes) compared with only 40% of placebo eyes. These results show that not only is the product effective in most patients, even those with severe symptoms, but relief is sustained for a long period.

Safety Confirmed

In a 6-week safety trial, more than 800 patients received either bepotastine besilate ophthalmic solution 1.5% or vehicle, 1 drop twice a day for 6 weeks. Investigators assessed visual acuity, slit lamp biomicroscopy, physical examinations, IOP, dilated ophthalmoscopy, noncontact specular microscopy, ocular comfort (as reported by patients at instillation and 5 minutes post instillation) and adverse events. They found no statistical difference between patients receiving bepotastine besilate ophthalmic solution 1.5% and those receiving placebo in eye irritation, headache or other issues; 25% of patients noticed a mild taste with bepotastine besilate ophthalmic solution 1.5%.

Also of note, on a scale of 0 to 3, more than 92% of the 6,400+ ocular comfort scores were 0, indicating that those patients/subjects had no discomfort from instillation of bepotastine besilate ophthalmic solution 1.5%. That’s important, because if an eye drop stings, patients may not be likely to use it. There were no clinically significant differences in ocular comfort between bepotastine besilate ophthalmic solution 1.5% and placebo after 1 or 3 weeks of dosing in the safety population.

Rapid, Durable Relief

In summary, bepotastine besilate ophthalmic solution 1.5% is a dual-acting antihistamine-mast cell stabilizer that is selective for the H1 receptor. It provides rapid, durable relief of ocular itching, and it has efficacy against a wide range of itch severity caused by a broad spectrum of allergens. It is comfortable on instillation and has a low incidence of adverse events.

Anyone who treats allergic conjunctivitis knows that no single therapy will alleviate all signs and symptoms in every case. Dr. Karpecki will discuss appropriate treatment for patients experiencing the late phase of the allergic response, when symptoms in addition to itching may be problematic.

References on page 7
The early phase of the allergic response involves predominantly histamine release from mast cells, resulting in significant itching, redness and chemosis. In the late phase, not only mast cells, but also basophils and eosinophils come into play. They are recruited to the conjunctival tissue where they release additional inflammatory mediators — platelet-activating factor, leukotrienes, prostaglandins, cytokines and chemokines — all of which exacerbate and perpetuate the immune response.\textsuperscript{5,11}

Although it may seem logical to choose a drug to treat allergic conjunctivitis based on the amount of time a patient has been symptomatic, establishing a time frame may be difficult. I make my treatment decision based on my clinical examination and the patient’s chief complaint. When a patient says, “I have a severe itching in my eye,” I prefer to prescribe a dual-acting antihistamine-mast cell stabilizer, such as bepotastine besilate ophthalmic solution 1.5% (Bepreve). If a patient has itching but is equally concerned about burning/stinging, chemosis and redness, I prescribe a steroid, loteprednol etabonate ophthalmic suspension 0.2% (Alrex), because steroids act at the level of the arachidonic acid pathway to block the production of prostaglandins and leukotrienes and have an indication for multi-symptom resolution including redness. I choose this specific steroid because it is indicated for temporary relief of signs of seasonal allergic conjunctivitis as well as symptoms.\textsuperscript{20} Most of the newer anti-histamine/mast cell stabilizers are indicated for either treatment of or prevention of itching associated with allergic conjunctivitis. The efficacy and safety of loteprednol 0.2% was examined in two identical, 6-week, randomized, double-masked, vehicle-controlled parallel-group multicenter studies.\textsuperscript{21,22}

### Efficacy and Safety

In studies performed at the Dell Laser Vision Center (n=133) and the Shulman Center (n=135), patients were randomly assigned to loteprednol 0.2% or vehicle administered 4 times a day for 42 days. The primary endpoints were bulbar injection and itching at 14 days.\textsuperscript{21,22}

Investigators at both sites reported significant reductions in the severity of bulbar injection in the treatment groups after 14 days. In the Dell study, resolution favored the drug over placebo, 31% and 9%, respectively; in the Shulman study, resolution favored the drug over placebo, 36% and...
Use of Steroid Drops in Practice

Practicing in a cornea specialty referral practice, I prescribe steroids frequently, but even after 20 years in practice, I’m cautious. Steroids are contraindicated in the presence of most viral conditions, such as herpes simplex, or an active infection, such as early bacterial keratitis or mycobacterium. As a precaution, I don’t write refills for steroids the first time I prescribe them to patients. I know if the drug is working well, which steroids typically do, and the patient has three refills, I may not see him for a long time, and I don’t want someone returning to my office in 3 or 4 months with elevated IOP. I also don’t recommend patients place the drop on top of a contact lens.

As you would expect, the prescribing information for loteprednol etabonate ophthalmic suspension 0.2% (Alrex) includes a precaution, advising practitioners to monitor IOP if the product is used for 10 or more days. In clinical trials, only one patient of a total of 133 patients treated with loteprednol 0.2% experienced an IOP rise ≥10 mm Hg.21,22 I have prescribed loteprednol thousands of times, and in my personal experience, the incidence of an IOP rise into the high-20 mm Hg range or higher is about 1% to 1.5%.

Loteprednol 0.2% is contraindicated in anyone with known hypersensitivity to any ingredient in it or to steroids. Being a C-20 ester steroid, loteprednol 0.2% has a proven safety profile, but in my opinion, it’s important to monitor patients for IOP rises, changes in vision, cataract formation and secondary ocular infections.

My advice is to strike a balance when considering a steroid. For patients with significant signs of allergic conjunctivitis, a short course of a steroid may be indicated, and as with every steroid, you should proceed with caution but also not withhold a steroid when indicated.

15%, respectively. Changes from baseline to 2 hours after treatment in both studies were remarkable.

The steroid also controlled itching, but the difference was not statistically significant until 2 to 3 days in the Dell study and 7 days in the Shulman study.

In both studies, the safety profile for loteprednol 0.2% was comparable to that of placebo. No patient in the Dell study had an IOP rise of 10 mm Hg or more from baseline. In the Shulman study, one patient in each group (drug and placebo) had an IOP rise of 10 mm Hg or more from baseline. For more on steroid use in an eyecare practice, see “Use of Steroid Drops in Practice” above.

Another interesting fact about loteprednol 0.2% — I think — is that it contains two moisturizing components, glycerin and povidone.

In summary, loteprednol 0.2% covers early- and late-phase inflammatory mediators. It provides temporary relief of the signs and symptoms associated with seasonal allergic conjunctivitis, including redness, burning, stinging, discomfort, foreign body sensation, tearing and itching. Its incidence of IOP elevations is comparable to vehicle, and it contains moisturizing ingredients. This combination of properties translates to a robust therapy in clinical practice.
Fast, Sustained Relief

Ocular allergy can be a stressful condition for patients, and once they are in your office — often after trying to resolve their symptoms on their own — they are seeking fast and sustained relief. Two of the most effective therapies we can prescribe are bepotastine 1.5% for first-line, year-round relief of itching associated with signs and symptoms of allergic conjunctivitis and loteprednol etabonate 0.2% for temporary, multisymptom relief in patients with seasonal allergic conjunctivitis.1

REFERENCES

1. IMS data
16. Muñiz M, Williams JI, Gow JA, Schoesley GL, McNamara TR; Bepotastine Ophthalmic Solutions Clinical Study Group. Bepotastine besilate ophthalmic solution 1.5% provides a rapid and sustained reduction in ocular itch for severely allergic subjects following exposure to ragweed or grass pollens using the conjunctival allergen challenge (CAC) model of allergic conjunctivitis. Poster presented at: 2011 Annual Scientific Meeting of the American College of Allergy, Asthma & Immunology; November 3-8, 2011; Boston, MA.
17. Clark JC, Williams JI, Gow JA, Abelson MB, McNamara TR; Bepotastine Besilate Ophthalmic Solutions Clinical Study Group. Bepotastine besilate ophthalmic solution 1.5% rapidly eliminates ocular itching in more severely allergic subjects in the conjunctival allergen challenge model of allergic conjunctivitis. Poster presented at: 24th Annual Eastern Allergy Conference; May 6-9, 2010; Palm Beach, FL.
20. Alrex® (loteprednol etabonate ophthalmic suspension) 0.2% prescribing information. Bausch & Lomb Incorporated; Tampa, FL. November 2011.
BEPREVE® (bepotastine besilate ophthalmic solution) 1.5% is a histamine H1 receptor antagonist used to treat contact lens-related irritation.

**WARNINGS AND PRECAUTIONS**
- To reduce the risk of contamination, avoid touching dropper tip to any surface. Keep bottle tightly closed when not in use. (5.1)
- BEPREVE should not be used to treat contact lens-related irritation. (5.2)
- Remove contact lenses prior to instillation of BEPREVE. (5.5)

**ADVERSE REACTIONS**
- The most common adverse reaction occurring in approximately 25% of patients was a mild taste following instillation. Other adverse reactions occurring in 2-5% of subjects were eye irritation, headache, and nasopharyngitis. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Bausch & Lomb Incorporated at 1-800-323-0000, or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

See 17 for PATIENT COUNSELING INFORMATION

**REFERENCES**

1. **INDICATIONS AND USAGE**
- BEPREVE is a histamine H1 receptor antagonist indicated for the treatment of itching associated with allergic conjunctivitis. (1)

2. **DOSAGE AND ADMINISTRATION**
- Instil one drop into the affected eye(eyes) twice a day (BID). (2)

3. **DOSAGE FORMS AND STRENGTHS**
- Solution containing bepotastine besilate 1.5%. (3)

4. **CONTRAINDICATIONS**
- BEPREVE is contraindicated in patients with a known hypersensitivity reactions to bepotastine besilate or any of the other ingredients. (4.1)

5. **WARNINGS AND PRECAUTIONS**
- Minimize the contaminating the dropper tip and solution, care should be taken not to touch the dropper tip or any surface with the dropper tip of the bottle. Keep bottle tightly closed when not in use. (5.1)

6. **CONTACT LENS USE**
- Patients should be advised not to wear a contact lens at bedtime or during the day that should not have been used to treat contact lens-related irritation. (6.1)

7. **GERIATRIC USE**
- No age-related differences in safety or effectiveness have been observed between elderly and younger patients. (8.5)

8. **USE IN SPECIFIC POPULATIONS**
- Pregnancy: Category C. Teratogenicity studies have been performed in animals. Bepotastine besilate was not found to be teratogenic in rats during organogenesis and fetal development at oral doses up to 200 mg/kg/day (representing a systemic concentration approximately 3,300 times that anticipated for topical ocular use in humans), but did show some potential for causing skeletal abnormalities in rats given 200 mg/kg/day, (8.1)

9. **USE IN SPECIFIC POPULATIONS**
- Pregnancy: Category C. Teratogenicity studies have been performed in animals. Bepotastine besilate was not found to be teratogenic in rats during organogenesis and fetal development at oral doses up to 200 mg/kg/day (representing a systemic concentration approximately 3,300 times that anticipated for topical ocular use in humans), but did show some potential for causing skeletal abnormalities in rats given 200 mg/kg/day, (8.1)

Bepotastine besilate is a white or pale yellowish crystalline powder. The molecular weight of bepotastine besilate is 547.08 daltons. BEPREVE® ophthalmic solution is supplied as a sterile, aqueous 1.5% solution, with a pH of 6.8. The composition of BEPREVE® (bepotastine besilate ophthalmic solution) 1.5% is approximately 290 mOsm/kg.

Each ml of BEPREVE® (bepotastine besilate ophthalmic solution) 1.5% contains: Bepotastine besilate 1.5 mg (equivalent to 10.7 mg bepotastine)

Preservative: benzalkonium chloride 0.005%

Inactive: monobasic sodium phosphate dihydrate, sodium chloride, sodium hydroxide to adjust pH, and water for injection, USP.

12. **CLINICAL PHARMACOLOGY**
- Bepotastine is a topically active, direct H1- receptor antagonist and an inhibitor of the release of histamine from mast cells.

13. **Pharmacokinetics**
- Absorption: The extent of systemic exposure to bepotastine following topical ophthalmic administration of bepotastine besilate 1% and 1.5% ophthalmic solutions was evaluated in 12 healthy adults. Following one drop of 1% or 1.5% bepotastine besilate ophthalmic solution to both eyes four times daily (TID) for seven days, bepotastine plasma concentrations peaked at approximately one to two hours post instillation. Maximum plasma concentration for the 1% and 1.5% ophthalmic solutions were 5.1 ± 2.5 pg/mL and 7.3 ± 1.9 pg/mL, respectively. Plasma concentration at 24 hours post-instillation was below the quantifiable limit (2 ng/mL) in 11/12 subjects in the two dose groups.
- Distribution: The extent of protein binding to bepotastine is approximately 56% and independent of bepotastine concentration.

14. **CLINICAL STUDIES**
- Clinical efficacy was evaluated in 2 conjunctival allergen challenge (CAC) studies (217 patients). BEPREVE® (bepotastine besilate ophthalmic solution) 1.5% was comparable to its vehicle for relieving ocular itching elicited by an ocular allergen challenge, both at a CAC 15 minutes post-dosing and a CAC 6 hours post-dosing of BEPREVE. The safety of BEPREVE was evaluated in a randomized clinical study of 861 subjects over a period of 6 weeks.

15. **HOW SUPPLIED/STORAGE AND HANDLING**
- For topical ophthalmic administration only. (16.1)

16. **STABILITY OF DROPPER TIP**
- Patients should be advised not to touch the dropper tip or any surface with the dropper tip of the bottle; the dropper tip should be returned to the bottle after each use. (16.2)

17. **PATIENT COUNSELING INFORMATION**
- For topical ophthalmic administration only. (17.1)

18. **STERILITY OF DROPPER TIP**
- Patients should be advised not to touch the dropper tip or any surface with the dropper tip of the bottle; the dropper tip should be returned to the bottle after each use. (16.2)

19. **CONCOMITANT USE OF CONTACT LENSES**
- Patients should be advised not to wear a contact lens at bedtime or during the day that should not have been used to treat contact lens-related irritation. (6.1)

20. **GERIATRIC USE**
- No age-related differences in safety or effectiveness have been observed between elderly and younger patients. (8.5)

21. **USE IN SPECIFIC POPULATIONS**
- Pregnancy: Category C. Teratogenicity studies have been performed in animals. Bepotastine besilate was not found to be teratogenic in rats during organogenesis and fetal development at oral doses up to 200 mg/kg/day (representing a systemic concentration approximately 3,300 times that anticipated for topical ocular use in humans), but did show some potential for causing skeletal abnormalities in rats given 200 mg/kg/day, (8.1)

22. **DOSAGE AND ADMINISTRATION**
- Instil one drop of BEPREVE® into the affected eye(s) twice a day (BID). (2)

23. **DOSAGE FORMS AND STRENGTHS**
- Solution containing bepotastine besilate 1.5%. (3)

24. **CONTRAINDICATIONS**
- BEPREVE is contraindicated in patients with a known hypersensitivity reactions to bepotastine besilate or any of the other ingredients. (4.1)

25. **WARNINGS AND PRECAUTIONS**
- Minimize the contaminating the dropper tip and solution, care should be taken not to touch the dropper tip or any surface with the dropper tip of the bottle. Keep bottle tightly closed when not in use. (5.1)

26. **CONTACT LENS USE**
- Patients should be advised not to wear a contact lens at bedtime or during the day that should not have been used to treat contact lens-related irritation. (6.1)

27. **GERIATRIC USE**
- No age-related differences in safety or effectiveness have been observed between elderly and younger patients. (8.5)

28. **USE IN SPECIFIC POPULATIONS**
- Pregnancy: Category C. Teratogenicity studies have been performed in animals. Bepotastine besilate was not found to be teratogenic in rats during organogenesis and fetal development at oral doses up to 200 mg/kg/day (representing a systemic concentration approximately 3,300 times that anticipated for topical ocular use in humans), but did show some potential for causing skeletal abnormalities in rats given 200 mg/kg/day, (8.1)

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- Instil one drop of BEPREVE® into the affected eye(s) twice a day (BID). (2)

30. **DOSAGE FORMS AND STRENGTHS**
- Solution containing bepotastine besilate 1.5%. (3)

31. **CONTRAINDICATIONS**
- BEPREVE is contraindicated in patients with a known hypersensitivity reactions to bepotastine besilate or any of the other ingredients. (4.1)

32. **WARNINGS AND PRECAUTIONS**
- Minimize the contaminating the dropper tip and solution, care should be taken not to touch the droppers tip or any surface with the dropper tip of the bottle. Keep bottle tightly closed when not in use. (5.1)

33. **CONTACT LENS USE**
- Patients should be advised not to wear a contact lens at bedtime or during the day that should not have been used to treat contact lens-related irritation. (6.1)

34. **GERIATRIC USE**
- No age-related differences in safety or effectiveness have been observed between elderly and younger patients. (8.5)

35. **USE IN SPECIFIC POPULATIONS**
- Pregnancy: Category C. Teratogenicity studies have been performed in animals. Bepotastine besilate was not found to be teratogenic in rats during organogenesis and fetal development at oral doses up to 200 mg/kg/day (representing a systemic concentration approximately 3,300 times that anticipated for topical ocular use in humans), but did show some potential for causing skeletal abnormalities in rats given 200 mg/kg/day, (8.1)
Information for Patients: This product is sterile when packaged. Patients should be advised not to allow the dropper tip to touch any surface, as this may contaminate the suspension. If redness or itching becomes aggravated, the patient should be advised to consult a physician. Patients should be advised not to wear a contact lens if their eye is red. ALEX® should not be used to treat contact lens related irritation. The preservative in ALEX®, benzalkonium chloride, may be absorbed by soft contact lenses. Patients who wear soft contact lenses and whose eyes are not red, should be instructed to wait at least ten minutes after instilling ALEX® before they insert their contact lenses.

Carcinogenesis, mutagenesis, impairment of fertility: Long-term animal studies have not been conducted to evaluate the carcinogenic potential of loteprednol etabonate.

Ocular adverse reactions include elevated intraocular pressure, which may rarely be associated with acute angle closure glaucoma in susceptible individuals. Systemic steroids appear in human milk, and could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. Caution should be exercised when ALEX® is administered to a nursing woman.

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

Adverse Reactions: Reactions associated with ophthalmic steroids include elevated intraocular pressure, which may rarely be associated with acute angle closure glaucoma in susceptible individuals. Systemic steroids appear in human milk, and could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. Caution should be exercised when ALEX® is administered to a nursing woman.

Storage: Store upright between 15°C–25°C (59°F–77°F). DO NOT FREEZE.

KEEP OUT OF REACH OF CHILDREN.

Revised November 2011.

Bausch & Lomb Incorporated, Tampa, Florida 33637

U.S. Patent No. 5,340,930

U.S. Patent No. 5,747,061

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