ARMED AGAINST ALLERGENS

Leading Strategies to Manage Today's **Allergic Conjunctivitis Patient**

REVIEW OF OPTOMETRY

BAUSCH + LOMB

Faculty

Paul M. Karpecki, OD, FAAO
Kentucky Eye Institute, Lexington, Kentucky
Gaddie Eye Centers, Louisville, Kentucky

Jimmy D. Bartlett, OD, FAAO
(Professor Emeritus) University of Alabama at Birmingham
Birmingham, Alabama

I. Ben Gaddie, OD, FAAO
Gaddie Eye Centers
Louisville, Kentucky

Marc Bloomenstein, OD, FAAO
Schwartz Laser Eye Center
Scottsdale, Arizona

Mel Friedman, OD, FAAO
For Your Eyes Only
Memphis, Tennessee

More than 50 million Americans suffer from allergies each year,[1] with up to 40% of individuals reporting ocular symptoms related to allergies.[2] Published data from countries around the world suggest that the scope of atopic diseases—including seasonal allergic conjunctivitis (SAC) and perennial allergic conjunctivitis (PAC)—has been increasing in prevalence in recent decades.[3]

U.S. healthcare costs related to allergic conjunctivitis, when grouped with allergic rhinitis, are reportedly as high as $5.9 billion, with 25% ($1.5 billion) tied to medication use.[4] Interestingly, ocular prescription medication expenditures jumped—from $6 million in the early 1990s to more than $200 million at the start of the new millennium.[4] This upsurge in medical prescriptions may have signaled the start of a movement away from patient self-medication and toward greater clinician involvement.

The reason why allergies, and specifically ocular allergies, are becoming more widespread across the United States is up for discussion. Some clinicians subscribe to the hygiene hypothesis, proposing that a lack of early childhood exposure to infections and reduced opportunities for unhygienic contact within families has led to an increase in the clinical expression of allergic and atopic diseases.[5]

If this hypothesis is correct, the ubiquitous presence of sanitizing agents—an industry expected to reach $1.6 billion in the global market by 2020, driven in large part by the country's vigorous response to highly publicized reports of global disease outbreaks and infectious diseases in recent years—will only propagate the problem.[6]

The path on which we arrived at the current state may not entirely be clear, but the persistent, pervasive expansion of ocular allergies is a situation in need of proactive attention by eye care professionals to address, manage and mitigate the ocular allergic burden. This highly esteemed panel of eye care professionals sheds light on strategies taking aim at ocular allergens.

– Paul M. Karpecki, OD, FAAO –

Allergen Assault: A Growing Gateway

Dr. Karpecki: *Given the information on the growth of allergies and ocular allergies, in particular, are there any reasons why we're seeing such an increase, especially in the United States?*

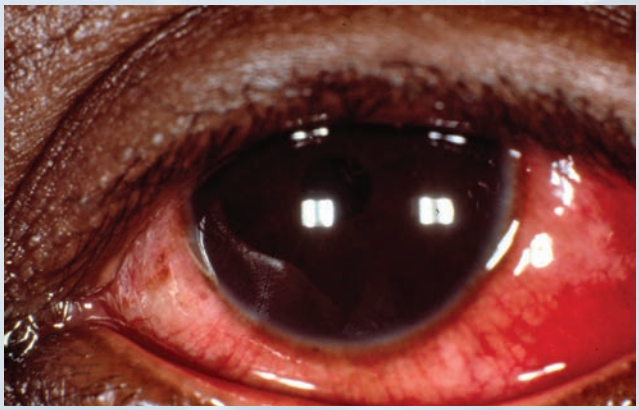
Dr. Bloomenstein: I subscribe to the hygiene hypothesis. Fifty years ago, children would go outside and play in the dirt, eat off of non-sanitized surfaces and build their immune system. Nowadays, people are using so much hand sanitizer that I believe children aren't able to develop the immunity they historically had.

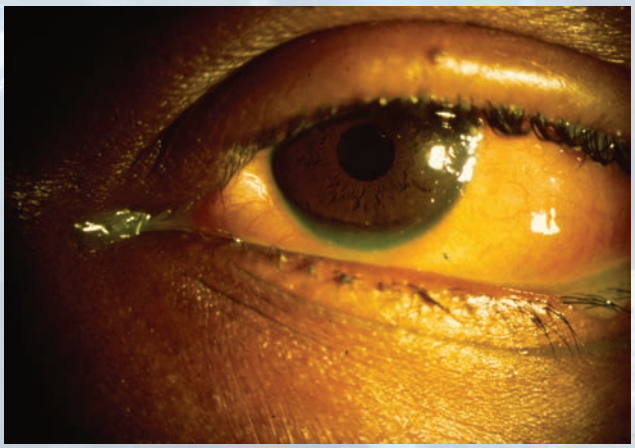
Dr. Bartlett: In addition, the increasing industrialization and pollution around us today exacerbates ocular surface disease, and an unstable or irritated ocular surface makes an allergy that much worse. So, the manifestations of allergies are more severe because of all of those factors working together.

Dr. Bloomenstein: We're also getting heightened variability in the weather and climate, which has shifted the course of seasonal allergies for patients, especially in the northern tiers of the United States. And the food we're

eating is injected with more chemicals.

Dr. Gaddie: Interestingly, older patients are starting to present with allergies. In the past, you would rarely see older individuals with allergy problems, since susceptibility tends to go down with age. Now, I'm routinely seeing people in their 70s and even 80s who never experienced allergies over the course of their lives, but are suddenly being diagnosed with seasonal and perennial allergic disease.





Conjunctival hyperemia, chemosis and lid edema associated with seasonal allergic conjunctivitis. Photos: Jimmy Bartlett, OD, FAAO

Making the Right Diagnosis

Dr. Karpecki: *When making a diagnosis of allergic conjunctivitis, what symptoms and signs do you look*

Doctor's Allergy Formula

Isolating Allergens to Target Therapy

Dr. Karpecki: Can you talk about Doctor's Allergy Formula™—a short, in-office ocular allergy diagnostic test utilizing a panel of allergens specific to different regions of the country and providing results within 10 to 15 minutes. The test launched in 2013 and is available for use by optometrists in a number of states, and many more are working on that opportunity for our profession.

Dr. Friedman: As a practitioner who is currently using Doctor's Allergy Formula™, I believe this point-of-care diagnostic test is going to alter the way we approach our ocular allergy patients. The test, which comes in a plastic container, is firmly rolled onto the skin of each arm so the allergen penetrates, and within 10 to 15 minutes you can see a reaction. Positive results are indicated by a 3mm-or-larger raised area. Importantly, the test can isolate specific allergens for which a patient has sensitivity. In my office, we have never had an anaphylactic reaction, possibly because we're testing allergens the patient is already encountering every day, but we are prepared with Benadryl and epinephrine in the event that we do. Once we pinpoint the specific allergen, we customize treatment and counsel the patient on what to avoid. Before now, we relied on symptoms and signs to diagnose allergies, and often used a shotgun approach to therapy. 'You have allergies, bam, we're going to give you this.' Now, we give patients the drugs they specifically need, and recommend they avoid allergen A, B and C, which further aids the treatment strategy.

Dr. Bloomenstein: Another advantage to the test is that if we're treating a dry eye patient who also has ocular allergies, and we're rolling into a seasonal allergy, we can start taking preventative or proactive measures.

Dr. Karpecki: *Is it correct that you just need a CLIA [Clinical Laboratory Improvement Amendments] waiver to perform this test?*

Dr. Friedman: Yes. I was actually audited last year by CLIA, and we not only passed, we got a letter of recommendation.

Dr. Bartlett: How has the reception been by allergists to the Doctor's Allergy Formula™ test?

Dr. Friedman: We're strictly speaking of ocular allergy. But, there's no reason why we can't do consults and make referrals to the allergist if necessary. We don't want to make this test a threatening point; the development of this technology should create some cohesion between the two professions.

Patient Case: Clearing AKC After Failed Attempts

A 34-year old male and professional golf instructor complained of an inability to go outside in the sunlight because he could not keep his eyes open due to burning, stinging and itching in both eyes. "People think I have pink eye and stay away," he said. The problem persisted for several years, and became worse over the previous winter season.

The patient unsuccessfully tried to relieve symptoms with cool compresses and flushing the eyes with water. He also used "allergy drops," prescribed by a physician, which he said helped with symptoms but did not clear the appearance of his eyes.

Slit-lamp and clinical exams revealed bilateral conjunctival redness and eyelid edema, periorbital redness and eczema, and superior corneal neovascularization with approximately 3mm to 4mm of encroachment. The anterior chamber was observed to be deep and quiet (D&Q), and the lens was clear. Diagnosis was determined to be atopic keratoconjunctivitis (AKC), a form of allergic conjunctivitis.

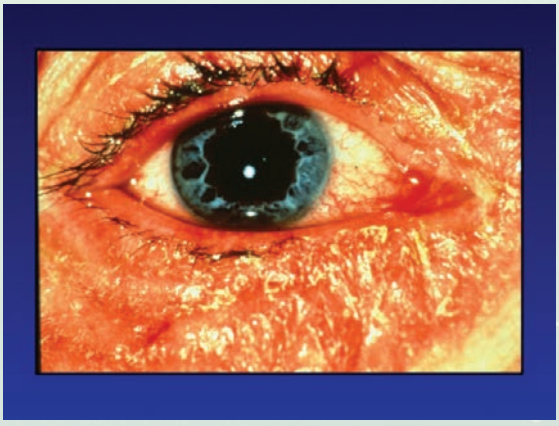


Photo: Paul M. Karpecki, OD, FAAO

Treatment included Bepreve® (bepotastine besilate ophthalmic solution 1.5%) BID for the patient's severe itch, a corticosteroid, preservative-free artificial tears p.r.n., cool compresses and patient education on allergy avoidance. The patient was also referred to an allergist.

Though he experienced exacerbations and remissions over the subsequent six months, the patient gradually recovered. No further corneal neovascularization developed, and aside from the occasional flare-up around the fall allergy season, the patient's condition is now stable.

for? I know we're taught that the symptom of ocular itch signifies allergy, but itching on the eyelids could be blepharitis or a host of other conditions, so it's potentially misleading.

Dr. Gaddie: Diagnosis of ocular allergies is a complicated scenario, and we're learning more about the level of complexity every day, but in general, I look for the classic symptoms that bring patients in most of the time. When patients tell me their eyes itch, I ask them to show me the exact location of the sensation, and they do one of two things: They take their finger or hand and start grinding in the corner of their eye, which suggests the problem might be allergies; or they take a finger and rub horizontally across their lid, which tells me the issue is probably a blepharitis or MGD [meibomian gland dysfunction] type of condition, potentially *Demodex*. Then, as part of my clinical exam, I'll look for other signs, such as swelling or chemosis, which is indicative of the acute phase of seasonal allergies, and papillae on the inner surface of the upper eyelid, which could signify GPC [giant papillary conjunctivitis], a common complication of contact lens wear. I also ask about a history of eye watering and overall irritation.

Dr. Bartlett: Many patients come in complaining about itching, and it's important to understand that symptoms of allergic conjunctivitis generally include bilateral itching, not just one eye. But often, other than the itch symptom, there will be no signs to note as part of the clinical workup. The slit-lamp exam may be totally normal, which means you must evaluate all of the anterior segment. You have to look at the lid margins, express the meibomian glands, assess the tear meniscus, stain the cornea, do tear breakup time, etc., to get you closer to diagnosis. Return patients will usually give you a history indicating that symptoms occur every fall or spring. When a patient is atopic, or genetically predisposed to hypersensitivity, there is almost always a family history of allergies,[7] and it's usually a multisystem manifestation of allergies affecting more than the eyes. It's very important that you ask the patient specifically about all medical conditions and a family history of allergies. But, in the absence of any positive signs, if itching is the primary complaint, that usually leads us to a diagnosis of allergic conjunctivitis.

Dr. Bloomenstein: I take it a step further. I'll ask a patient, "Do you have burning in your eyes?" Dr. Milton Hom published a paper showing the comorbidity of dryness and allergy, and oftentimes clinicians will misdiagnose allergy as dry eye, or conversely dry eye as allergy.[8] So I'll highlight specifically, "Do you have any itching and burning, or do you have itching and tearing?" Traditionally, I will see itching and tearing as more of an allergic response, while burning will prompt me to look at the lid margin, maybe consider demodicosis or other conditions that could cause the itch. I do tear osmolarity as a way of differentiating the diagnosis. In a normal reading, I'm moving away from dry eye and toward allergy; a higher result will lead me toward dry eye.

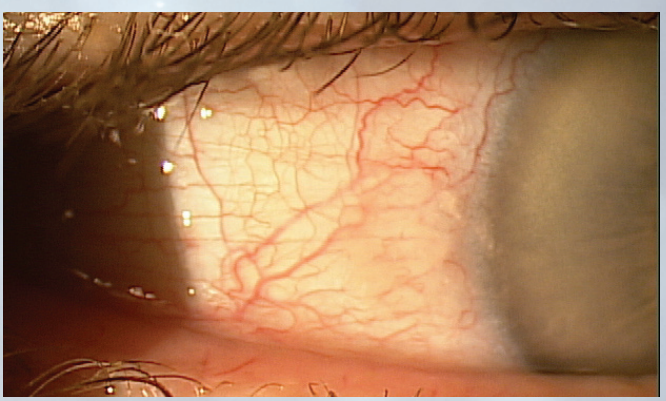
Dr. Karpecki: A big differentiator for me is the presence of allergic rhinitis. You don't normally see rhinitis in dry eye patients as a matter of course, but you see it in many patients with ocular allergies. Also, if you ever see elevation at the limbus—accumulation of eosinophils and presence of limbal nodules, extended for as little as one clock hour—along with other signs of a more serious chronic allergy condition, that's no longer seasonal allergic conjunctivitis; it's vernal keratoconjunctivitis, and clinicians can miss those subtle signs.

Dr. Friedman: Being a contact lens practice, we talk to patients about the discomfort they might be experiencing with their contact lenses. Individuals might complain of a stringy, white discharge; itchy eyes or contact lens shifting during blinking. When I hear the contact lenses are moving, I'm going to inspect underneath the lid for papillae to see if the patient might have a GPC issue, which is very common in contact lens abusers. So, I'm looking at symptoms and at signs to diagnose the patient, and finding that allergy today has become much more prevalent, but it's not as obvious as it used to be.

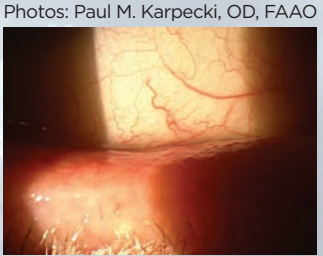
Seasonal vs. Perennial Allergies

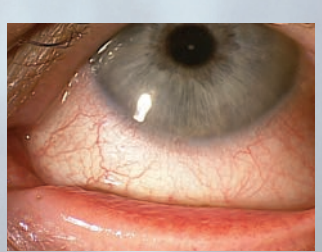
Dr. Karpecki: *With regard to the two most common types of ocular allergies—seasonal and perennial—can you discuss how they intersect, the changing landscape today and whether there is any benefit to distinguishing between these two disease categories from a treatment or management perspective?*

Dr. Bartlett: There's a lot of overlap between season-



Papillae present in a patients with seasonal allergic conjunctivitis (SAC).
Photos: Paul M. Karpecki, OD, FAAO





al and perennial allergies. If you look at the southern tiers of the United States, what is considered seasonal allergies anywhere else in the country becomes a year-round issue. On the other hand, if you think of traditional perennial allergens such as mold and animal dander, those can be an acute manifestation for many people. With animal dander, the problem only occurs when the person is exposed to a cat or dog, for example, which could be infrequently. So, those individuals have acute allergic conjunctivitis whereas the owners of those same pets would have year-round allergies.

Dr. Gaddie: Where I live in Kentucky, we get a lot of rainfall and frequently have moderate temperatures, so mold can be present not only from rainwater, but also from old water damage in the home. We see a lot of mold-related allergies that can be perennial because they're in the house.

Dr. Bloomenstein: It almost seems like we now have a continuum of allergies—even in the temperate climates.

Dr. Friedman: Years ago, clinicians used to recommend asthmatics move to states in the Southwest like Arizona because of the dry weather. But asthmatics don't do as well there as they used to—not because the weather isn't still dry, but likely because of the growing allergy problem, which doesn't respect borders.

Dr. Karpecki: From a management perspective, if I can identify that allergies are seasonal, I might schedule a patient for an exam a month or two ahead of the next projected onset, in contrast with perennial allergy patients, who I want to monitor on a regular basis because they experience symptoms all year long, with periodic exacerbations. However, the treatment strategy relies more on the signs, symptoms and presentation than it does on perennial vs. seasonal.

Dr. Bartlett: The therapeutics of ocular allergy really doesn't depend upon differentiating the two. You look at the patient's manifestations and go from there. So whether it's seasonal or perennial almost is irrelevant.

The Cascade

Dr. Karpecki: *Let's talk about the allergic cascade, its phases and how we as eye care professionals understand and respond to the complex sequence of inflammatory events triggered by the presence of an allergen and subsequent immune response activation due to an incorrectly perceived threat.[9] We'll start with an explanation of what happens in the early acute phase, occurring seconds or minutes after a patient comes into contact with an allergen, and then move on to the late phase, beginning four to six hours after exposure.*

Dr. Bartlett: After initial exposure to the allergen during the early phase, the immune system overreacts by producing immunoglobulin E (IgE) antibodies that bind to

Palliative Measures

Dr. Karpecki: In addition to pharmaceutical strategies, are there palliative treatment options and recommendations that you make for your allergy patients?

Dr. Bloomenstein: Many of us are familiar with recommending warm compresses for meibomian gland dysfunction, but I think we, as optometrists, should also think about suggesting cool compresses for allergy patients. Moreover, I talk about trying to avoid the allergens, and above all else, I encourage patients to keep the eyes lubricated. I think having a good tear film helps to reduce the amount of antigens on the ocular surface.

Dr. Karpecki: I suggest my allergy patients use preservative-free tears to avoid aggravation of an already atopic individual.

Dr. Bartlett: Many allergists have been suggesting for years that patients wash their hair before they go to bed to remove any environmental allergens, such as tree pollen, from the hair that might be introduced to the bed linens. For mold allergies, people can remove carpet and transition to a hard-surface flooring.

Dr. Karpecki: Some people sleep with ceiling fans every night, which kicks up allergens during certain times of the year, and it disseminates dust year-round. I tell patients to turn the fan to a low setting, or better yet, shut it off during the offending seasons. Look at the pollen levels. If you're prone to outdoor allergies, stay inside on the high-count days and run on the treadmill, or just use logical approaches to avoid flare-ups.

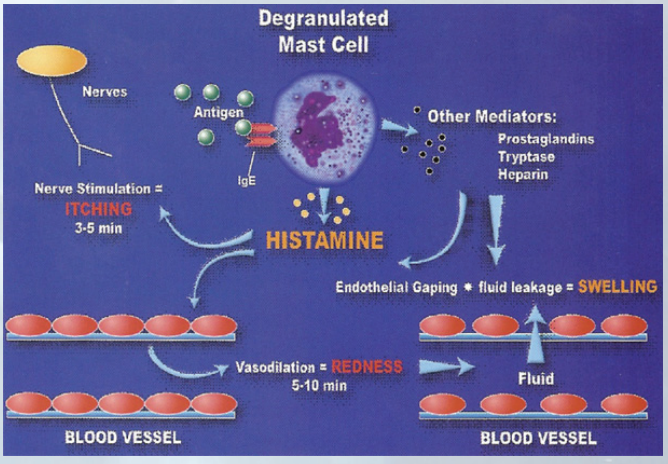


Image: John L. Schachet, OD

mast cells and basophils. Ongoing exposure leads to the release of chemical mediators (e.g., histamine, prostaglandin, tryptase and heparin) that cause the symptoms of allergy—a process known as mast cell degranulation.[10] In the cascade's late phase, other cells (e.g., eosinophils, neutrophils and lymphocytes) arrive at the site of contact, prompting red, swollen tissues. Cytokines released by the mast cells and basophils act as messengers to recruit cells to the inflamed area. TH2 lymphocytes discharge additional cytokines attracting more inflammatory cells—in particular eosinophils, which release chemicals that damage the tissues and promote continued inflammation for heightened sensitivity.[10] Relative to the eye specifically, as histamine travels to the vascular beds and activates H2 receptors, it produces vasodilatation and red, swollen tissues, contributing to the classic symptom of red eye. The dilated blood vessel is leaky, so interior fluid exudes into the tissues, leading to swelling. Thirdly, the histamine travels to the nerve endings, stimulating H1 receptors and giving rise to the itch effect. That's why H1 antagonists target itching. Chymase and tryptase, proteins secreted by the mast cells that promote inflammation, have been shown to also activate goblet cells to create mucus.[11,12] The increased mucus in the tear film often yields a stringy discharge that many patients with ocular allergies experience.

Dr. Bloomenstein: Unfortunately for us as clinicians, we don't tend to see many patients at the acute phase or for an unknown period of time afterwards. It appears that many patients are self-diagnosing and self-medicating.

Targeted Treatments for the Early Phase

Dr. Karpecki: *During the acute phase and shortly thereafter, patients routinely present with itching as a hallmark symptom due to release of histamine and other mediators. The H1 antagonists are primarily in-*

Please see Important Safety Information for BEPREVE® (bepotastine besilate ophthalmic solution) on page 5 and ALREX® (loteprednol etabonate ophthalmic suspension) on page 6 and full Prescribing Information for BEPREVE® and ALREX® on pages 12-15.

Tips to Prevent Eye Allergies

Avoidance is one of the best ways to avoid triggering eye allergies. Other tips from the Asthma and Allergy Foundation of America include:

- Don't touch or rub the eye(s)
- Wash hands often with soap and water
- Use a vacuum with a HEPA filter to reduce exposure to allergens
- Wash bed linens and pillowcases in hot water and detergent to reduce allergens
- Use allergen covers (encasements) for pillows, comforters, duvets and mattresses, and consider using them for box springs
- Keep pets out of the bedroom to reduce pet dander allergen in bedding
- Wear sunglasses and a wide-brimmed hat to help keep pollen from getting into the eyes
- Close windows during high-pollen and mold seasons. Run the air conditioner in the car and at home, and consider using a HEPA filter.

Eye Allergies (Allergic Conjunctivitis). Asthma and Allergy Foundation of America. Available at: http://www.aafa.org/page/eye-allergy-conjunctivitis.aspx (last accessed March 23,2016).

dicated for itch. How do you address this stage of the cascade therapeutically?

Dr. Bartlett: When the patient's primary presentation is itch response, and there's little, if any, swelling, with a fairly normal conjunctiva, that's the H1 effect. So it makes sense from a therapy standpoint to antagonize that effect. We do that with H1 blockers, many of which are available topically. A 2015 Cochran review—a large, broad-based, rigorous approach to literature review—stated that all available H1 antagonists on the market for ophthalmic therapy are effective.[13] Furthermore, if you can simultaneously stabilize the mast cell—and our new products will do that, as they are dual-acting—you get less degranulation.

Dr. Gaddie: At our practice, we see two sets of allergy patients: new patients who present with acute onset allergy, and others we've managed for years who we know have seasonal allergies and allergic conjunctivitis. For the latter group, we recommend that individuals stay on something like Bepreve® (bepotastine besilate 1.5%), an antihistamine/mast cell stabilizer, during those trigger seasons so we can keep the mast cell from degranulating and having histamine release, thereby controlling the itch symptom.

Dr. Karpecki: One important feature of this medication for me is the itch data that came out of a demanding conjunctival allergen challenge (CAC) trial. As part of a sub-analysis of two randomized studies examining patients with severe ocular itch at baseline, 68% of Bepreve®-treated eyes (n=104) achieved complete relief of ocular itch vs. 3% of placebo-treated eyes (n=98 eyes) measured at three minutes post-allergen challenge ($p<0.0001$), with drug instillation 15 minutes prior to the challenge.[14]

Dr. Friedman: We will actually take patients off oral antihistamines to halt the associated anti-muscarinic effect triggering decreased mucous and aqueous secretion manifesting in dry eyes and mouth, and alternately target itch with Bepreve®, which does not have significant binding affinity for muscarinic receptors that may cause these side effects.[15,*] Another feature of Bepreve® that hasn't been mentioned is the low benzalkonium chloride level, at 0.005%.

Late-Phase Interventions

Dr. Karpecki: *The later phase involving leukotrienes, prostaglandins and platelet-activating factor manifesting in the signs of allergy indicates a different management course than the early phase since we're dealing with inflammatory mediators. The H1 antagonists don't have specific agents to target inflammatory markers, such as redness and chemosis. Can you talk about your approach to managing the late phase? When do you turn to corticosteroids? And is your decision based on late-phase signs or severity of the presentation?*

Dr. Gaddie: The more signs of inflammation I see, the more likely a steroid is going to be indicated vs. just an antihistamine/mast cell stabilizer. Other atopic findings around the eye will also lead me in the direction of a steroid.

*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.

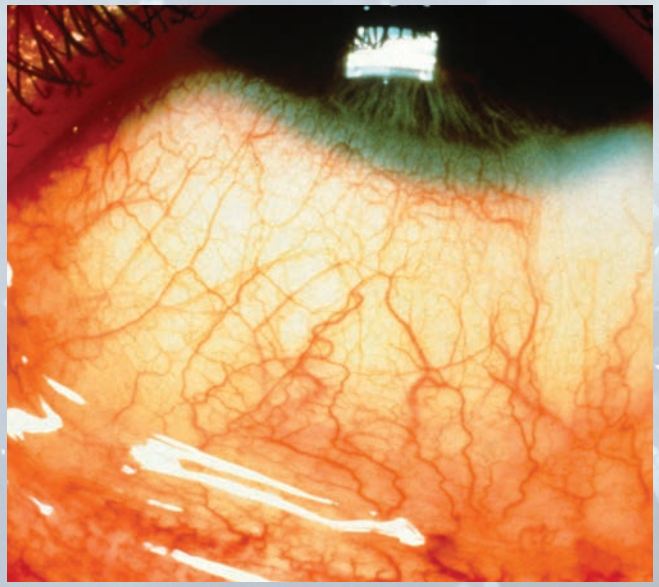
Dr. Bloomenstein: A product like Alrex® (loteprednol etabonate 0.2%), a topical corticosteroid indicated for temporary relief of signs and symptoms of SAC, would be my go-to for the late-phase signs associated with SAC, since I know that I'm helping the patient manage the inflammatory load.

Dr. Gaddie: One of the features I like about Alrex® is the formulation contains glycerin and povidone, two known moisturizers. So when I use a steroid, that's the one I prefer.

Dr. Bartlett: As a rule, we always want to prescribe steroids for the shortest period of time necessary. That being said, the patient's IOP should be monitored at 10 or more days of use with the product. According to the drug's prescribing information, the physician should only initiate a medication order of Alrex® and any order renewal beyond 14 days, after a patient exam aided by magnification.

Paradigm Shift Toward Corticosteroids

Dr. Karpecki: *No more than a decade ago, many optometrists avoided prescribing topical corticosteroids for SAC due to concerns about IOP elevation, cataract development or other potential side effects. Can you talk about your practices concerning corticosteroids in eye care and the hesitation by some professionals to embrace these anti-inflammatory agents?*



Typical conjunctival hyperemia in a patient with moderately severe seasonal allergic conjunctivitis. Photos: Jimmy Bartlett, OD, FAAO

"I think the paradigm shift over the last decade in the treatment of allergic conjunctivitis has been toward use of steroids as first-line agents. That's something that many optometrists and some ophthalmologists still haven't learned. They continue to use a linear model where you start with an antihistamine/mast cell stabilizer first for itch associated with allergic conjuntivitis, and if that doesn't work, then you go to a steroid. But I think we've gotten beyond that."

- Dr. Bartlett

Dr. Bartlett: I think the paradigm shift over the last decade in the treatment of allergic conjunctivitis has been toward use of steroids as first-line agents. That's something that many optometrists and some ophthalmologists still haven't learned. They continue to use a linear model where you start with an antihistamine/mast cell stabilizer first for itch associated with allergic conjuntivitis, and if that doesn't work, then you go to a steroid. But I think we've gotten beyond that. Patients can achieve considerable immediate relief by going with the steroid as a first-line treatment for SAC. This strategy would be geared more toward severe itching, or the individual who has signs along with itching. Once we've established steroid use is warranted, we shouldn't tiptoe into the water in our prescribing protocols.

Closing the Loop With Follow-Up

Dr. Karpecki: *We have all heard anecdotally about some clinicians who don't follow up with ocular allergy patients after placing them on medications, perhaps because of the high success rate of some newer formulations. Can you talk about the significance of tracking the patient during and upon conclusion of therapeutic intervention, and offer wisdom on best practices?*

Dr. Bloomenstein: We have a responsibility as clinicians to not only define signs and symptoms for patients and prescribe appropriate treatment, but also to conduct ongoing monitoring during and post-therapy. It's an active way of evaluating results as well as any possible negative effects. The ocular allergy bur-

den is a perfect opportunity for us as optometrists to follow through: You start a patient on a treatment and don't just leave it there. You bring them back in, make sure the plan is working and set them on an alternative course if it's not.

Dr. Gaddie: Not only do you want to follow up with patients, but if signs and symptoms are advancing rapidly in a specific case, you may also want to bring the individual back sooner; the time frame depends to a degree on the severity of the allergy presentation.

Dr. Karpecki: There is also the issue of compliance to consider with respect to follow-up and timing of the next visit. If a patient is at risk of noncompliance, I will require the person to come back sooner for evaluation than a more responsible patient. Usually, I will forego refills. If the patient is truly at a high risk of noncompliance, I sometimes avoid steroids altogether. It's essential to get to know our patients beyond just looking at their eyes and prescribing drugs. You can assess who is more likely to be compliant just by certain discussions you have.

Getting to Know the Patient

Dr. Bloomenstein: As eye care professionals, we need to have proactive discussions with new and existing patients about allergies. We should make sure that we're asking upfront: Do you have times during the year when your eyes start to get more irritated or tear? Maybe even have the staff involved, or post placards in the front of the office indicating this is an ocular allergy center. We talk a lot about dry eye centers to the exclusion of other eye diseases.

Dr. Karpecki: As part of our office intake form to determine which patients have dry eye symptoms, I recently added questions to uncover potential ocular allergy indicators: Do you suffer from allergies, or do you ever have itchy eyes?

Dr. Gaddie: Our office also has new patients fill out a questionnaire before they see us, and we have been surprised by the number of people reporting symptoms of ocular allergy.

Dr. Friedman: And many of these patients are already self-medicating. Studies over the last decade have found that a high percentage of patients who seek clinical evaluation for various ocular conditions are using over-the-counter medications after presumably self-diagnosing their symptoms.[16,17] If individuals come into our offices, and they're looking for our expert opinion and guidance, and we send them back out the door with nothing beyond the OTC drug they are already using, we've done them a disservice. It is up to us to treat them professionally.

Dr. Karpecki: Many patients will turn to oral OTC antihistamines to treat their allergic conjunctivitis thinking that's what pharmacists recommend. It's ingrained in their minds based on what they see, read and hear in the public sphere, and if you don't bring it up specifically, they probably won't even mention that they are taking these OTC drugs.

Dr. Gaddie: That is why it is imperative to inquire about prescribed and OTC medicines. If a patient is taking an oral antihistamine, probe further: Do you have allergies? Are you taking any other OTC or prescription medications for the problem? Do your eyes itch? Usually, they'll say, 'Yes, my eyes itch, but I'm on Claritin®.' And that's the opportunity to educate the patient that they may need a prescription for a topical medication.

Dr. Karpecki: We have a lot of educating to do with our patient base on allergic conjunctivitis in order to get to the root of each patient's problem and ultimately get control of a growing and constantly evolving ocular allergy phenomenon that shows no sign of slowing down.

1. Allergies. Centers for Disease Control and Prevention. Available at: http://www.cdc.gov/healthcommunication/ToolsTemplates/EntertainmentEd/Tips/Allergies.html (last accessed March 15, 2016).

2. Singh K, Axelrod S, Bielory L. The epidemiology of ocular and nasal allergy in the United States. 1988–1994. *J Allergy Clin Immunol*. 2010;126(4):778-83.

3. Gomes PJ. Trends in prevalence and treatment of ocular allergy. *Curr Opin Allergy Clin Immunol*. 2014;14(5):451-6.

4. Bielory L. Update on ocular allergy treatment. *Expert Opin Pharmacother*. 2002 May;3(5):541-53.

5. Strachan DP. Family size, infection and atopy: the first decade of the "hygiene hypothesis". *Thorax*. 2000;55 Suppl 1:S2-10.

6. Hand Sanitizers Market Trends. "The Global Hand Sanitizers Market: Trends, Drivers & Projections." Global Industry Analysts, Inc. April 2015. Available at: http://www.strategyr.com/MarketResearch/Hand_Sanitizers_Market_Trends.asp (last accessed March 15, 2016).

7. Thomsen SF, Ulrik CS, Kyvik KO, et al. Findings on the atopic triad from a Danish twin registry. *Int J Tuberc Lung Dis*. 2006;10(11):1268-72.

8. Hom MM, Nguyen AL, Bielory L. Allergic conjunctivitis and dry eye syndrome. *Ann Allergy Asthma Immunol*. 2012;108(3):163-6.

9. Overview of the Immune System. National Institute of Allergy and Infectious Diseases. Available at: https://www.niaid.nih.gov/topics/immuneSystem/Pages/overview.aspx (last accessed March 16, 2016).

10. Allergic Cascade. MedicineNet. Available at: http://www.medicinenet.com/allergic_cascade/page4.htm (last accessed March 16, 2016).

11. Caughey GH. Mast cell tryptases and chymases in inflammation and host defense. *Immunol Rev*. 2007;217:141-54.

12. Runge MS, Patterson C. eds. *Principles of Molecular Medicine 2nd ed*. Totowa, NJ: Humana Press; 2016.

13. Castillo M, Scott NW, Mustafa MZ, et al. Topical antihistamines and mast cell stabilisers for treating seasonal and perennial allergic conjunctivitis. Cochrane Database Syst Rev. 2015;Jun 1;6:CD009566.

14. Meier EJ, Torkildsen GL, Gow JA. Integrated phase III trials of bepotastine besilate ophthalmic solution 1.5% for ocular itching associated with allergic conjunctivitis. Allergy Asthma Proc. 2012 May-Jun;33(3):265-74.

15. Kato M, Nishida A, Aga Y, et al. Pharmacokinetic and pharmacodynamic evaluation of central effect of the novel antiallergic agent betotastine besilate. *Arzneimittelforschung*. 1997;47(10):1116-24.

16. Clegg JP, Guest JF, Lehman A. The annual cost of dry eye syndrome in France, Germany, Italy, Spain, Sweden and the United Kingdom among patients managed by ophthalmologists. *Ophthalmic Epidemiol*. 2006;13(4):263-74.

17. Marquez GE, Torres VE, Sanchez VM, et al. Self-medication in ophthalmology: a questionnaire-based study in an Argentinean population. *Ophthalmic Epidemiol*. 2012;19(4):236-41.

Please see Important Safety Information for BEPREVE® (bepotastine besilate ophthalmic solution) on page 5 and ALREX® (loteprednol etabonate ophthalmic suspension) on page 6 and full Prescribing Information for BEPREVE® and ALREX® on pages 12-15.

BEPREVE®
(bepotastine besilate
ophthalmic solution) 1.5%

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use BEPREVE® (bepotastine besilate ophthalmic solution) 1.5% safely and effectively. See full prescribing information for BEPREVE®.
BEPREVE® (bepotastine besilate ophthalmic solution) 1.5%
Initial U.S. Approval: 2009

----------RECENT MAJOR CHANGES----------
Contraindications (4) 06/2012

----------INDICATIONS AND USAGE----------
BEPREVE® is a histamine H_1 receptor antagonist indicated for the treatment of itching associated with allergic conjunctivitis. (1)

---------- DOSAGE AND ADMINISTRATION ----------
Instill one drop into the affected eye(s) twice a day (BID). (2)

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

---------- CONTRAINDICATIONS----------
Hypersensitivity to any component of this product. (4)

---------- 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)
- BEPREVE should not be used to treat contact lens-related irritation. (5.2)
- Remove contact lenses prior to instillation of BEPREVE. (5.2)

----------ADVERSE REACTIONS----------
The most common adverse reaction occurring in approximately 25% of patients was a mild taste following instillation. Other adverse reactions which occurred in 2-5% of subjects were eye irritation, headache, and nasopharyngitis. (6)

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

Revised: 10/2012

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
5.1 Contamination of Tip and Solution
5.2 Contact Lens Use
5.3 Topical Ophthalmic Use Only
6 ADVERSE REACTIONS
6.1 Clinical Trial Experience
6.2 Post-Marketing Experience
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.3 Pharmacokinetics
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis and Impairment of Fertility
14 CLINICAL STUDIES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION
17.1 Topical Ophthalmic Use Only
17.2 Sterility of Dropper Tip
17.3 Concomitant Use of Contact Lenses

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE
BEPREVE® (bepotastine besilate ophthalmic solution) 1.5% is a histamine H_1 receptor antagonist indicated for the treatment of itching associated with signs and symptoms of allergic conjunctivitis.

2 DOSAGE AND ADMINISTRATION
Instill one drop of BEPREVE into the affected eye(s) twice a day (BID).

3 DOSAGE FORMS AND STRENGTHS
Topical ophthalmic solution containing bepotastine besilate 1.5%.

4 CONTRAINDICATIONS
Bepreve is contraindicated in patients with a history of hypersensitivity reactions to bepotastine or any of the other ingredients *[see Adverse Reactions (6.2)]*.

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. BEPREVE should not be used to treat contact lens-related irritation.
BEPREVE should not be instilled while wearing contact lenses. Remove contact lenses prior to instillation of BEPREVE. The preservative in BEPREVE, benzalkonium chloride, may be absorbed by soft contact lenses. Lenses may be reinserted after 10 minutes following administration of BEPREVE.
5.3 Topical Ophthalmic Use Only
BEPREVE is for topical ophthalmic use only.

6 ADVERSE REACTIONS
6.1 Clinical Trials Experience
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.
The most common reported adverse reaction occurring in approximately 25% of subjects was a mild taste following instillation. Other adverse reactions occurring in 2-5% of subjects were eye irritation, headache, and nasopharyngitis.
6.2 Post Marketing Experience
Hypersensitivity reactions have been reported rarely during the post-marketing use of BEPREVE. Because these reactions are reported voluntarily from a population of unknown size, it is not always possible to reliably estimate their frequency or establish a casual relationship to drug exposure. The hypersensitivity reactions include itching, body rash, and swelling of lips, tongue and/or throat.

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
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 at 1,000 mg/kg/day. There were no teratogenic effects seen in rabbits at oral doses up to 500 mg/kg/day given during organogenesis and fetal development (>13,000 times the dose in humans on a mg/kg basis). Evidence of infertility was seen in rats given oral bepotastine besilate 1,000 mg/kg/day; however, no evidence of infertility was observed in rats given 200 mg/kg/day (approximately 3,300 times the topical ocular use in humans). The concentration of radio-labeled bepotastine besilate was similar in fetal liver and maternal blood plasma following a single 3 mg/kg oral dose. The concentration in other fetal tissues was one-third to one-tenth the concentration in maternal blood plasma.
An increase in stillborns and decreased growth and development were observed in pups born from rats given oral doses of 1,000 mg/kg/day during perinatal and lactation periods. There were no observed effects in rats treated with 100 mg/kg/day.
There are no adequate and well-controlled

studies of bepotastine besilate in pregnant women. Because animal reproduction studies are not always predictive of human response, BEPREVE® (bepotastine besilate ophthalmic solution) 1.5% should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

8.3 Nursing Mothers

Following a single 3 mg/kg oral dose of radiolabeled bepotastine besilate to nursing rats 11 days after delivery, the maximum concentration of radioactivity in milk was 0.40 mcg-eq/mL 1 hour after administration; at 48 hours after administration the concentration was below detection limits. The milk concentration was higher than the maternal blood plasma concentration at each time of measurement.

It is not known if bepotastine besilate is excreted in human milk. Caution should be exercised when BEPREVE (bepotastine besilate ophthalmic solution) 1.5% is administered to a nursing woman.

8.4 Pediatric Use

Safety and efficacy of BEPREVE (bepotastine besilate ophthalmic solution) 1.5% have not been established in pediatric patients under 2 years of age. Efficacy in pediatric patients under 10 years of age was extrapolated from clinical trials conducted in pediatric patients greater than 10 years of age and from adults.

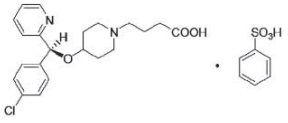
8.5 Geriatric Use

No overall difference in safety or effectiveness has been observed between elderly and younger patients.

11 DESCRIPTION

BEPREVE (bepotastine besilate ophthalmic solution) 1.5% is a sterile, topically administered drug for ophthalmic use. Each mL of BEPREVE contains 15 mg bepotastine besilate.

Bepotastine besilate is designated chemically as (+) -4-[[(S)-p-chloro-alpha -2-pyridylbenzyl]oxy]-1-piperidine butyric acid monobenzenesulfonate. The chemical structure for bepotastine besilate is:



Bepotastine besilate is a white or pale yellowish crystalline powder. The molecular weight of bepotastine besilate is 547.06 daltons. BEPREVE® ophthalmic solution is supplied as a sterile, aqueous 1.5% solution, with a pH of 6.8.

The osmolality of BEPREVE (bepotastine besilate ophthalmic solution) 1.5% is approximately 290 mOsm/kg.

Each mL of BEPREVE® (bepotastine besilate ophthalmic solution) 1.5% contains:

Active:

Bepotastine besilate 15 mg (equivalent to 10.7 mg bepotastine)

Preservative: benzalkonium chloride 0.005%

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

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Bepotastine is a topically active, direct H_1-receptor antagonist and an inhibitor of the release of histamine from mast cells.

12.3 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 (QID) for seven days, bepotastine plasma concentrations peaked at approximately one to two hours post-instillation. Maximum plasma concentration for the 1% and 1.5% strengths were 5.1 ± 2.5 ng/mL and 7.3 ± 1.9 ng/mL, respectively. Plasma concentration at 24 hours post-instillation were below the quantifiable limit (2 ng/mL) in 11/12 subjects in the two dose groups.

Distribution: The extent of protein binding of bepotastine is approximately 55% and independent of bepotastine concentration.

Metabolism: *In vitro* metabolism studies with human liver microsomes demonstrated that bepotastine is minimally metabolized by CYP450 isozymes.

In vitro studies demonstrated that bepotastine besilate does not inhibit the metabolism of various cytochrome P450 substrate via inhibition of CYP3A4, CYP2C9, and CYP2C19. The effect of bepotastine besilate on the metabolism of substrates of CYP1A2, CYP2C8, CYP2D6 was not studied. Bepotastine besilate has a low potential for drug interaction via inhibition of CYP3A4, CYP2C9, and CYP2C19.

Excretion: The main route of elimination of bepotastine besilate is urinary excretion (with approximately 75-90% excreted unchanged in urine).

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis and Impairment of Fertility

Long-term dietary studies in mice and rats were conducted to evaluate the carcinogenic potential of bepotastine besilate. Bepotastine besilate did not significantly induce neoplasms in mice receiving a nominal dose of up to 200 mg/kg/day for 21 months or rats receiving a nominal dose of up to 97 mg/kg/day for 24 months. These dose levels represent systemic exposures approximating 350 and 200 times that achieved with human topical ocular use.

The no observable adverse effect levels for bepotastine besilate based on nominal dose levels in carcinogenicity tests were 18.7 to 19.9 mg/kg/day in mice and 9.6 to 9.8 mg/kg/day in rats (representing exposure margins of approximately 60 and 20 times the systemic exposure anticipated for topical ocular use in humans).

There was no evidence of genotoxicity in the Ames test, in CHO cells (chromosome aberrations), in mouse hepatocytes (unscheduled DNA synthesis), or in the mouse micronucleus test.

When oral bepotastine was administered to male and female rats at doses up to 1,000 mg/kg/day, there was a slight reduction in fertility index and surviving fetuses. Infertility was not seen in rats given 200 mg/kg/day oral bepotastine besilate (approximately 3,300 times the systemic concentration anticipated for topical ocular use in humans).

14 CLINICAL STUDIES

Clinical efficacy was evaluated in 2 conjunctival allergen challenge (CAC) studies (237 patients). BEPREVE (bepotastine besilate ophthalmic solution) 1.5% was more effective than its vehicle for relieving ocular itching induced by an ocular allergen challenge, both at a CAC 15 minutes post-dosing and a CAC 8 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.

16 HOW SUPPLIED/STORAGE AND HANDLING

BEPREVE® (bepotastine besilate ophthalmic solution) 1.5% is supplied in a white low density polyethylene plastic squeeze bottle with a white controlled dropper tip and a white polypropylene cap in the following size:

5 mL (NDC 24208-629-02)
10 mL (NDC 24208-629-01)

STORAGE

Store at 15° – 25°C (59° – 77°F).

17 PATIENT COUNSELING INFORMATION

17.1 Topical Ophthalmic Use Only

For topical ophthalmic administration only.

17.2 Sterility of Dropper Tip

Patients should be advised to not touch dropper tip to any surface, as this may contaminate the contents.

17.3 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 BEPREVE should not be used to treat contact lens-related irritation.

Patients should also be advised to remove contact lenses prior to instillation of BEPREVE. The preservative in BEPREVE, benzalkonium chloride, may be absorbed by soft contact lenses. Lenses may be reinserted after 10 minutes following administration of BEPREVE.

Manufactured by: Bausch & Lomb Incorporated
Tampa, FL 33637
Under license from:
Senju Pharmaceutical Co., Ltd.
Osaka, Japan 541-0046

9291000 (flat)
9291100 (folded)

BAUSCH + LOMB

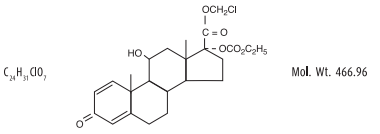
Alrex®

loteprednol etabonate
opthalmic suspension 0.2%

STERILE OPHTHALMIC SUSPENSION

Rx only

DESCRIPTION
ALREX® (loteprednol etabonate ophthalmic suspension) contains a sterile, topical anti-inflammatory corticosteroid for ophthalmic use. Loteprednol etabonate is a white to off-white powder.
Loteprednol etabonate is represented by the following structural formula:



$C_{24}H_{31}ClO_7$ Mol. Wt. 466.96

Chemical Name:
chloromethyl 17α-[(ethoxycarbonyl)oxy]-11β-hydroxy-3-oxoandrosta-1,4-diene-17β-carboxylate

Each mL contains:
ACTIVE: Loteprednol Etabonate 2 mg (0.2%);
INACTIVES: Edetate Disodium, Glycerin, Povidone, Purified Water and Tyloxapol. Hydrochloric Acid and/or Sodium Hydroxide may be added to adjust the pH. The suspension is essentially isotonic with a tonicity of 250 to 310 mOsmol/kg.
PRESERVATIVE ADDED: Benzalkonium Chloride 0.01%.

CLINICAL PHARMACOLOGY
Corticosteroids inhibit the inflammatory response to a variety of inciting agents and probably delay or slow healing. They inhibit the edema, fibrin deposition, capillary dilation, leukocyte migration, capillary proliferation, fibroblast proliferation, deposition of collagen, and scar formation associated with inflammation. There is no generally accepted explanation for the mechanism of action of ocular corticosteroids. However, corticosteroids are thought to act by the induction of phospholipase A_2 inhibitory proteins, collectively called lipocortins. It is postulated that these proteins control the biosynthesis of potent mediators of inflammation such as prostaglandins and leukotrienes by inhibiting the release of their common precursor arachidonic acid. Arachidonic acid is released from membrane phospholipids by phospholipase A_2. Corticosteroids are capable of producing a rise in intraocular pressure.

Loteprednol etabonate is structurally similar to other corticosteroids. However, the number 20 position ketone group is absent. It is highly lipid soluble which enhances its penetration into cells. Loteprednol etabonate is synthesized through structural modifications of prednisolone-related compounds so that it will undergo a predictable transformation to an inactive metabolite. Based upon *in vivo* and *in vitro* preclinical metabolism studies, loteprednol etabonate undergoes extensive metabolism to inactive carboxylic acid metabolites.

Results from a bioavailability study in normal volunteers established that plasma levels of loteprednol etabonate and Δ^1 cortienic acid etabonate (PJ 91), its primary, inactive metabolite, were below the limit of quantitation (1 ng/mL) at all sampling times. The results were obtained following the ocular administration of one drop in each eye of 0.5% loteprednol etabonate 8 times daily for 2 days or 4 times daily for 42 days. This study suggests that limited (<1 ng/mL) systemic absorption occurs with ALREX.

Clinical Studies:
In two double-masked, placebo-controlled six-week environmental studies of 268 patients with seasonal allergic conjunctivitis, ALREX, when dosed four times per day was superior to placebo in the treatment of the signs and symptoms of seasonal allergic conjunctivitis. ALREX provided reduction in bulbar conjunctival injection and itching, beginning approximately 2 hours after instillation of the first dose and throughout the first 14 days of treatment.

INDICATIONS AND USAGE
ALREX Ophthalmic Suspension is indicated for the temporary relief of the signs and symptoms of seasonal allergic conjunctivitis.

CONTRAINDICATIONS
ALREX, as with other ophthalmic corticosteroids, is contraindicated in most viral diseases of the cornea and conjunctiva including epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, and varicella, and also in mycobacterial infection of the eye and fungal diseases of ocular structures. ALREX is also contraindicated in individuals with known or suspected hypersensitivity to any of the ingredients of this preparation and to other corticosteroids.

WARNINGS
Prolonged use of corticosteroids may result in glaucoma with damage to the optic nerve, defects in visual acuity and fields of vision, and in posterior subcapsular cataract formation. Steroids should be used with caution in the presence of glaucoma.

Prolonged use of corticosteroids may suppress the host response and thus increase the hazard of secondary ocular infections. In those diseases causing thinning of the cornea or sclera, perforations have been known to occur with the use of topical steroids. In acute purulent conditions of the eye, steroids may mask infection or enhance existing infection.

Use of ocular steroids may prolong the course and may exacerbate the severity of many viral infections of the eye (including herpes simplex). Employment of a corticosteroid medication in the treatment of patients with a history of herpes simplex requires great caution.

PRECAUTIONS
General: For ophthalmic use only. The initial prescription and renewal of the medication order beyond 14 days should be made by a physician only after examination of the patient with the aid of magnification, such as slit lamp biomicroscopy and, where appropriate, fluorescein staining.

If signs and symptoms fail to improve after two days, the patient should be re-evaluated.

If this product is used for 10 days or longer, intraocular pressure should be monitored.

Fungal infections of the cornea are particularly prone to develop coincidentally with long-term local steroid application. Fungus invasion must be considered in any persistent corneal ulceration where a steroid has been used or is in use. Fungal cultures should be taken when appropriate.

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. ALREX should not be used to treat contact lens related irritation. The preservative in ALREX, 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 ALREX 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. Loteprednol etabonate was not genotoxic *in vitro* in the Ames test, the mouse lymphoma tk assay, or in a chromosome aberration test in human lymphocytes, or *in vivo* in the single dose mouse micronucleus assay. Treatment of male and female rats with up to 50 mg/kg/day and 25 mg/kg/day of loteprednol etabonate, respectively, (1500 and 750 times the maximum clinical dose, respectively) prior to and during mating did not impair fertility in either gender.

Pregnancy: Teratogenic effects: Pregnancy Category C. Loteprednol etabonate has been shown to be embryotoxic (delayed ossification) and teratogenic (increased incidence of meningocele, abnormal left common carotid artery, and limb flexures) when administered orally to rabbits during organogenesis at a dose of 3 mg/kg/day (85 times the maximum daily clinical dose), a dose which caused no maternal toxicity. The no-observed-effect-level (NOEL) for these effects was 0.5 mg/kg/day (15 times the maximum daily clinical dose). Oral treatment of rats during organogenesis resulted in teratogenicity (absent innominate artery at ≥5 mg/kg/day doses, and cleft palate and umbilical hernia at ≥50 mg/kg/day) and embryotoxicity (increased postimplantation losses at 100 mg/kg/day and decreased fetal body weight and skeletal ossification with ≥50 mg/kg/day). Treatment of rats with 0.5 mg/kg/day (15 times the maximum clinical dose) during organogenesis did not result in any reproductive toxicity. Loteprednol etabonate was maternally toxic (significantly reduced body weight gain during treatment) when administered to pregnant rats during organogenesis at doses of ≥5 mg/kg/day.

Oral exposure of female rats to 50 mg/kg/day of loteprednol etabonate from the start of the fetal period through the end of lactation, a maternally toxic treatment regimen (significantly decreased body weight gain), gave rise to decreased growth and survival, and retarded development in the offspring during lactation; the NOEL for these effects was 5 mg/kg/day. Loteprednol etabonate had no effect on the duration of gestation or parturition when administered orally to pregnant rats at doses up to 50 mg/kg/day during the fetal period.

There are no adequate and well controlled studies in pregnant women. ALREX Ophthalmic Suspension should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known whether topical ophthalmic administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in human milk. 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 ALREX 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 be associated with optic nerve damage, visual acuity and field defects, posterior subcapsular cataract formation, secondary ocular infection from pathogens including herpes simplex, and perforation of the globe where there is thinning of the cornea or sclera.

Ocular adverse reactions occurring in 5-15% of patients treated with loteprednol etabonate ophthalmic suspension (0.2% - 0.5%) in clinical studies included abnormal vision/blurring, burning on instillation, chemosis, discharge, dry eyes, epiphora, foreign body sensation, itching, injection, and photophobia. Other ocular adverse reactions occurring in less than 5% of patients include conjunctivitis, corneal abnormalities, eyelid erythema, keratoconjunctivitis, ocular irritation/pain/discomfort, papillae, and uveitis. Some of these events were similar to the underlying ocular disease being studied.

Non-ocular adverse reactions occurred in less than 15% of patients. These include headache, rhinitis and pharyngitis.

In a summation of controlled, randomized studies of individuals treated for 28 days or longer with loteprednol etabonate, the incidence of significant elevation of intraocular pressure (≥10 mm Hg) was 2% (15/901) among patients receiving loteprednol etabonate, 7% (11/164) among patients receiving 1% prednisolone acetate and 0.5% (3/583) among patients receiving placebo. Among the smaller group of patients who were studied with ALREX, the incidence of clinically significant increases in IOP (≥10 mm Hg) was 1% (1/133) with ALREX and 1% (1/135) with placebo.

DOSAGE AND ADMINISTRATION

SHAKE VIGOROUSLY BEFORE USING.
One drop instilled into the affected eye(s) four times daily.

HOW SUPPLIED

ALREX® (loteprednol etabonate ophthalmic suspension, 0.2%) is supplied in a plastic bottle with a controlled drop tip in the following sizes:
5 mL (NDC 24208-353-05)
10 mL (NDC 24208-353-10)

DO NOT USE IF NECKBAND IMPRINTED WITH "Protective Seal" AND YELLOW IS NOT INTACT.

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

KEEP OUT OF REACH OF CHILDREN.

Revised: August 2013.

Bausch & Lomb Incorporated, Tampa, Florida 33637

9007904 (Folded)
9005504 (Flat)

ARMED AGAINST **ALLERGENS**