TREATMENT OF SEASONAL ALLERGIC CONJUNCTIVITIS  

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Allergic conjunctivitis affects approximately 15% of the global population and has a higher prevalence of about 40% in industrialized countries such as the United States. Seasonal allergy sufferers present with a variety of signs and symptoms, but patients frequently report that ocular allergy symptoms are the most bothersome. Many topical ocular prescription therapies are available and are increasingly prescribed due to patient demand for effective resolution of ocular allergy symptoms. Corticosteroid-based therapies such as loteprednol etabonate 0.2%, which act at a high level on the inflammatory cascade and thus broadly inhibit many inflammatory mediators, offer temporary relief of the signs and symptoms associated with seasonal allergic conjunctivitis.

T he allergic diseases that affect the eye include seasonal allergic conjunctivitis (SAC), also known as “hay fever,” perennial allergic conjunctivitis, giant papillary conjunctivitis, vernal keratoconjunctivitis, and atopic keratoconjunctivitis. The clinical manifestations of these allergic conditions range from mild to severe, with varying durations. The most common ocular allergy, SAC, affects patients predominantly during the spring or autumn, and is manifested by ocular itching, redness, tearing, foreign body sensation, photophobia, and discharge. Some SAC patients are affected for a few weeks to months during the year, while others have symptoms that last year-round. Although the ocular component is often the predominant disabling manifestation of seasonal allergies, they can also affect the nose, sinuses, ears, lungs, and skin. Recent studies have shown that ocular allergy symptoms significantly reduce quality of life, decrease work productivity, and place a substantial burden on the healthcare system. Because of SAC prevalence and its impact on patient quality of life, including the detrimental effects on contact lens wearers, it is imperative that optometrists have a good grasp on the diagnosis and clinical management of SAC.

**Seasonal Allergic Conjunctivitis**

**Etiology and Diagnosis**

Seasonal allergic conjunctivitis is an immunoglobulin E (IgE)-mediated hypersensitivity response triggered by airborne allergens such as pollen. Antigen binding to IgE receptors on mast cells causes immediate release of histamine, prostaglandins, leukotrienes, and proteolytic enzymes. This response occurs 20–40 minutes after antigen exposure and manifests clinically as itching, redness, swelling, and tearing. Mast cell degranulation results in activation of vascular endothelial cells and recruitment of other pro-inflammatory cells, such as eosinophils, neutrophils, and T cells, into the conjunctival mucosa. The infiltration of pro-inflammatory cells and subsequent release of additional inflammatory mediators by these cells 6–8 hours after antigen exposure is the basis for the potentiation and exacerbation of the inflammation, pain, and discomfort associated with the allergic response.

SAC diagnosis is based on patient history coupled with a clinical examination. The ocular symptoms may be the only findings, or the patient may also present with or have a history of concurrent nasal and ocular symptoms, a disease state known as allergic rhinoconjunctivitis. Seasonal symptoms are an important diagnostic clue, reflecting patient reactions to increased levels of allergens such as pollen or grasses during the spring, summer, or autumn.

**Indication:** ALREX® Ophthalmic Suspension is indicated for the temporary relief of the signs and symptoms of seasonal allergic conjunctivitis.

Please see Important Risk Information on page 4.
Allergic conjunctivitis usually affects both eyes to a similar degree and symptoms invariably include mild to severe itching. Ocular burning, redness, foreign body sensation, the presence of a stringy or watery discharge, and photophobia are other common manifestations. The bulbar conjunctiva may be hyperemic and/or chemotic, but in many cases there are no discernible clinical signs or evidence of abnormality. The key diagnostic feature of ocular allergy is ocular itching, with or without any demonstrable clinical signs. In most cases of allergic conjunctivitis, the cornea is rarely involved and vision remains unaffected.

Differential diagnosis must include some of the same clinical presentations as seen in allergic conjunctivitis, including dry eye, blepharitis, and meibomian gland dysfunction.

**Treatment Options**

Ocular allergy treatment is based on patient symptoms and overall severity of clinical presentation and should always be tailored to the specific needs of each patient. Initial SAC treatment regimens most often include a topical antihistamine or mast cell stabilizer to promote relief of symptoms associated with histamine release when cold compresses and artificial tears do not bring sufficient relief. For patients with moderate-to-severe or persistent SAC signs and symptoms, corticosteroids administered either alone or together with antihistamines or a dual-acting antihistamine/mast cell stabilizer may be useful. Novel therapeutic approaches, including sublingual immunotherapy, are on the horizon and may improve the care of millions of SAC patients.

For patients who do not experience symptom relief from antihistamines or mast cell stabilizers, topical corticosteroids represent the most comprehensive pharmacologic therapy.

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**Figure 1.** Loteprednol etabonate (LE) 0.2% provides temporary relief of seasonal allergic conjunctivitis symptoms by acting on both the early- and late-phase allergic response. Treatment with LE 0.2% decreases the production of inflammatory proteins, stabilizes mast cell membranes, and suppresses inflammatory cell infiltration. GM-CSF=granulocyte-macrophage colony-stimulating factor; Ig=immunoglobulin; IL=interleukin; PAF=platelet-activating factor; VCAM=vascular cell adhesion molecule. Adapted from Gelfand EW et al.
available by targeting the top level of the inflammatory cascade for effective treatment of both early and late phase ocular allergy symptoms. Corticosteroids regulate protein synthesis through activation of glucocorticoid receptors, which can directly or indirectly alter transcription and affect mRNA stability. Steroids thus inhibit the inflammatory process by decreasing the production of inflammatory proteins, histamine, and arachidonic acid, the precursor of prostaglandins and leukotrienes. Steroids also suppress proliferation and migration of inflammatory cells, such as eosinophils and lymphocytes, and stabilize mast cell membranes. By modulating the availability of pro-inflammatory factors, corticosteroids decrease the capacity for histamine, prostaglandin, and leukotriene release by mast cells during the early phase of the allergic response. Steroids also decrease inflammation associated with the late-phase allergic response by inhibiting inflammatory cell infiltration into ocular tissues. Because of their top-level and multimodal mechanism of action, steroids may provide broad relief of the many signs and symptoms associated with SAC (Figure 1). However, long-term use of topical ocular steroids has noted potential for adverse side effects, including increased intraocular pressure (IOP), steroid-induced glaucoma, development of cataracts, and increased risk for ocular infections.

A decade ago, the prevailing philosophy in the treatment of SAC was to use a stepped-care approach, in which initial therapy was followed by more aggressive treatment in the absence of sufficient improvement. Steroids were typically reserved for patients with moderate to severe symptoms, despite the use of topical ocular antihistamines, mast cell stabilizers, or dual-mechanism agents. Due to the potential for ocular and systemic adverse events, including increased IOP and cataract formation, the use of topically applied ocular corticosteroids in the treatment of SAC has varied. However, many practitioners now recommend steroid treatment as first-line management for moderate to severe symptoms either alone or in addition to antihistamines or in combination with antihistamine/mast cell stabilizer-based therapies for recurrent symptoms. Therefore, it is important to select a corticosteroid developed for the treatment of seasonal ocular allergies.

Loteprednol Etabonate in SAC Symptom Management

While some clinicians avoid corticosteroids because of possible ocular complications, others have fully embraced certain corticosteroids such as loteprednol etabonate (LE) 0.2% because of its proven efficacy and established safety profile for routine care of the SAC patient. Although LE has the same mechanism of action as other steroids, its structure has an important difference. Loteprednol etabonate is derived from the parent molecule

Please see Important Risk Information on page 4.
prednisolone, and is designed to facilitate rapid hydrolysis of the molecule to an inactive metabolite through a single metabolic inactivation step by endogenous esterase enzymes found in most tissues of the eye. Loteprednol etabonate 0.2% has shown a low risk and incidence of adverse events, specifically elevated IOP, because unbound LE is rapidly metabolized. Additionally, LE lacks a ketone moiety, making posterior subcapsular cataract formation due to LE use unlikely. With an established safety profile demonstrating IOP elevations similar to placebo, LE 0.2% is suitable for the treatment of ocular inflammatory symptoms of SAC.

**Clinical Studies in SAC**

Loteprednol etabonate 0.2% is currently the only ophthalmic corticosteroid specifically developed, tested, and US Food and Drug Administration-approved for SAC symptom treatment. Results from several clinical trials have demonstrated efficacy and safety of LE 0.2% for the treatment of SAC. Schulman and colleagues evaluated 135 patients during a 6-week study in which all patients received either LE 0.2% or placebo (vehicle) 4 times daily in both eyes. The primary sign evaluated was bulbar injection, and the primary symptom was itching. The secondary endpoints, including discomfort, foreign body sensation, burning, stinging, photophobia, palpebral conjunctival injection, chemosis and erythema, were also assessed after 2 weeks of treatment. Both the severity of bulbar injection (1.5 vs 1.0 units on a 0–3 scale) and itching (3.4 vs 3.0 units on a 0–4 scale) were significantly reduced for the LE 0.2% treatment group compared to placebo, in the first 2 weeks. More patients in the LE 0.2% treatment group than in the placebo group also experienced complete relief of symptoms at day 14 (36% and 15%; 58% and 38%, for injection and itching, respectively). Over the course of the study, LE 0.2% was significantly more effective than placebo in the treatment of SAC, with a safety profile comparable to placebo. Dell and colleagues conducted a similar study in 133 patients who were treated bilaterally 4 times daily for 42 days. The primary sign, bulbar injection, and primary symptom, itching, were significantly diminished in the LE treatment group compared

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**Important Risk Information**

- **ALREX®** 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 the 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.

- Prolonged use of ALREX® is associated with several WARNINGS and PRECAUTIONS, including glaucoma with optic nerve damage, defects in visual acuity, cataract formation, secondary ocular infections, exacerbation or prolongation of viral ocular infections (including herpes simplex), delay in wound healing and increase in bleb formation.

- If this product is used for 10 days or longer, intraocular pressure should be monitored. 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. Fungal infections of the cornea may develop with prolonged use of corticosteroids.

- 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.

- Please see complete information regarding CONTRAINDICATIONS, WARNINGS, PRECAUTIONS and ADVERSE REACTIONS in the accompanying ALREX® full prescribing information.
to placebo (1.3 vs 0.9 units on a 0–3 scale and 3.5 vs 3.1 units on a 0–4 scale for bulbar injection and itching, respectively). Secondary symptoms were also significantly reduced for the LE 0.2% treatment group vs the placebo group at day 14 for redness and discomfort (P<0.001). Importantly, no patient in either treatment group had significant IOP elevation. In clinical studies, adverse reactions that occurred in 5%–15% of LE patients included abnormal vision/blurring, burning on instillation, chemosis, discharge, dry eyes, epiphora, foreign body sensation, itching, injection, and photophobia. Overall, LE 0.2% was significantly more effective than placebo in the treatment of SAC signs and symptoms.

**Clinical Safety Profile**

Loteprednol etabonate 0.2% has an established safety profile. Novack and colleagues found that the incidence of significant IOP elevations with long-term (≥28 days) use of LE 0.2% was only 0.8%, similar to that for patients treated with placebo (vehicle). In contrast, the incidence of significant IOP elevations occurring with prednisolone acetate 1% was 6.7%. The optometrist should recognize that acute IOP elevations are possible with any steroid, including LE 0.2%. Thus, careful follow-up and monitoring of IOP are standard care for every patient on steroid therapy. Follow-up can be conducted from 1–5 days after initial examination, depending on the severity of patient symptoms, and should be aimed at determining efficacy of the treatment regimen. If LE 0.2% is used beyond 14 days, renewal of the medication order should be made only after patient examination with the aid of magnification.

**Conclusions**

Antihistamines alone or dual-acting antihistamine/mast cell stabilizers are often given as the initial therapy for SAC. However, steroids such as LE 0.2% are becoming more frequently prescribed earlier or as the initial treatment for more severe SAC symptoms or with antihistamines for persistent symptoms. By acting at the top-level of the inflammatory cascade, LE 0.2% has proven efficacy to treat the multiple downstream branches of resulting symptoms, including, itching, redness, burning/stinging, discomfort, swelling, tearing, photophobia, foreign body sensation, and discharge, with a low incidence of IOP similar to placebo. Therefore, optometrists can consider LE 0.2% as a viable option to effectively treat the broad range of symptoms associated with SAC.

Please see the full prescribing information for Alrex® on the following pages.
References
16. Lu E, Fujimoto LT, Vegabul PA, Jew RL. Steroid-induced ocular hypertension with loteprednol etabonate 0.2%—a case report. Optometry. 2011;82(7):413-420.

Disclosures
Dr. Bartlett serves as a paid consultant for Bausch & Lomb, ISTA Pharmaceuticals, and Allergan Pharmaceuticals. He also serves on speakers bureaus for Bausch & Lomb Pharmaceuticals and ISTA Pharmaceuticals. Drs. Thomas and Melton are members of the advisory group for Bausch & Lomb and serve on speakers bureaus for Alcon, Carl Zeiss, and Icare USA.

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PH4212 02/12
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:

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

Each ml contains:
ACTIVE: Loteprednol Etabonate 2 mg (0.2%);
INACTIVES: Edetate Disodium, Glycerin, Povidone, Purified Water and Tryptoan, Hydrochloric Acid and/or Sodium Hydroxide may be added to adjust the pH to 3.4-5.5. The suspension is essentially isotonic with a tonicity of 250 to 310 mOSM/kg.

PRESERVATIVE: ADDED: Benzoic Acid 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, 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. 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 clinical 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 its main metabolite (99%), 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 or 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. Fungal 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 (83 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, and cleft palatate and umbilical hernia at ≥50 mg/kg/day) and embroyotoxicity (increased post-implantation 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. AUREX 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 AUREX 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 uveal infection from pathogens including herpes simplex, and perforation of the globe where there is thinning of the cornea or sclera.

Oracular 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 or stinging, 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 edema, keratitis/conjunctivitis, ocular irritation/pain/discomfort, papillae, and uveitis. Some of these events were similar to the underlying ocular disease being studied.

Non-oracular 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% (1/583) among patients receiving placebos. Among the smaller group of patients who were studied with AUREX, the incidence of clinically significant increase in IOP (≥10 mm Hg) was 1% (1/113) with AUREX and 1% (1/135) with placebo.

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

HOW SUPPLIED:
AUREX* (loteprednol etabonate ophthalmic suspension, 0.2%) is supplied in a plastic bottle with a controlled drop tip in the following strengths:
5 ml (NDC 24208-353-03) - AB35307
10 ml (NDC 24208-353-10) - AB35309

DO NOT USE IF NECK BAND IMPRINTED WITH "Protective Seal and Yellow IS NOT INTACT."

Storage: Store up to 25°C (77°F). DO NOT FREEZE.

KEEP OUT OF REACH OF CHILDREN.

Revised August 2008.

Bausch & Lomb Incorporated, Tampa, Florida 33637
U.S. Patent No. 4,996,335
U.S. Patent No. 5,440,039
U.S. Patent No. 5,747,061
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90079902 (folded)
9005502 (flat)