LACRISERT®
(hydroxypropyl cellulose ophthalmic insert)

Reconsidering LACRISERT® (hydroxypropyl cellulose ophthalmic insert): An Overlooked Opportunity to Manage Moderate to Severe Dry Eye Disease

Highlights of a roundtable discussion held August 5th, 2019

PARTICIPANTS:

Participants are paid consultants of Bausch + Lomb

Derek Cunningham, OD, FAAO
is director of optometry and research at Dell Laser Consultants in Austin, TX.

Paul Karpecki, OD, FAAO
***Moderator,** is director of cornea services at Kentucky Eye Institute in Lexington, KY.*

Douglas Devries, OD
is co-founder and a practicing optometrist at Eye Care Associates of Nevada in Sparks, NV.

Margie Recalde, OD, FAAO
is a dry eye specialist and owner of Lifetime Optometric in Fresno, CA.

INTRODUCTION

Tear supplementation is a fundamental therapeutic strategy for patients with dry eye disease (DED).[1] Although LACRISERT, a unique, preservative-free, slow-release artificial tear, has been available for decades and is a central part of many patients' moderate to severe DED treatment regimens, younger patients and practitioners may be unaware of it. This supplement presents the perspectives and clinical experiences of a panel of experts on the opportunity LACRISERT presents for treating moderate to severe DED.

DIAGNOSTIC APPROACH

Paul Karpecki

To start broadly, how do you approach dry eye diagnosis and staging in day-to-day practice?

Douglas Devries

I start every patient, new or established, with the Standardized Patient Evaluation of Eye Dryness (SPEED) questionnaire. Based on their responses, I may initiate specific point-of-care tests: tear osmolarity, matrix metalloproteinase-9 (MMP-9), or meibography. The test results are then used to help decide whether patients should be directed to our dry eye clinic, where their disease can be classified based on severity.

Derek Cunningham

My practice uses a similar approach, though we primarily care for patients who present as candidates for cataract or refractive surgery, populations known to have high rates of preexisting DED.[2,3] We also use the SPEED questionnaire, as it helps cover the important questions and gather baseline symptom data. To ensure that we identify and manage DED in surgical candidates, we rigorously assess them all in our dry eye clinic. In an age of wavefront-guided technology and presbyopia-correcting intraocular lenses (IOLs), DED is a major contributing factor to patient dissatisfaction after cataract and refractive surgery.[4,5]

Margie Recalde

My approach is to discuss DED symptoms at the initial visit and schedule a separate dry eye workup. I also use the SPEED questionnaire but add the question "Does your vision fluctuate, and if so, how often?" as I have found this to be a recurring theme among patients with DED.

Please see Important Safety Information on page 2 and full Prescribing Information for LACRISERT® on page 4.

Paul Karpecki

After establishing a DED diagnosis, how do you differentiate subtypes of the disease (ie, evaporative, aqueous deficient, or both)?

Douglas Devries

A typical cause of evaporative DED is tear film lipid deficiency resulting from meibomian gland dysfunction (MGD).[6] To assess meibomian gland function, we use meibography and digital expression. Both methods are important—I've observed turbid or discolored meibum in patients whose meibography appears normal. But I think it is important to recognize that DED is a continuum, with most patients experiencing some degree of both aqueous deficiency and evaporative etiologies.[7]

Derek Cunningham

I agree. Almost all DED patients have combined aqueous deficient and evaporative DED, and both components and the associated inflammation need to be treated.[6] Ocular surface lubrication is an important starting point for DED of all subtypes.

ARTIFICIAL TEARS IN DED TREATMENT

Paul Karpecki

Let's discuss the role of tear supplementation. What is the importance of artificial tears, especially in moderate to severe DED?

Derek Cunningham

Tear supplementation is beneficial at every stage of DED. While artificial tears may not address the underlying cause(s) of DED, they provide crucial symptom relief. That said, many patients have trouble remembering to use drops or are reluctant to interrupt their work or other activities to do so. Because of these challenges, we need to look for ways to make tear supplementation work more easily into patients' lives, and that is where we find LACRISERT to be most helpful. The insert offers patients with moderate to severe DED a chance to have tear supplementation throughout the day, without the hassle of frequent dosing.

Douglas Devries

One reason for noncompliance with tears in patients with moderate to severe DED is the lack of discomfort symptoms due to decreased corneal

sensitivity. Those affected by corneal hypoesthesia are often unaware of the need to put in drops until they start to experience vision symptoms associated with DED.

Margie Recalde
I agree that tear supplementation is beneficial at all stages of DED, and and shouldn't be ignored in severe cases. As a preservative-free option with less frequent dosing, LACRISERT® (hydroxypropyl cellulose ophthalmic insert) can also help reduce moderate to severe DED patients' overall preservative load and improve treatment adherence.

> *"Some of my patients with moderate to severe DED may use LACRISERT exclusively, while for others it is adjunctive to other therapies"*

Paul Karpecki
Being preservative-free is undeniably a critical consideration for patients with moderate to severe DED. Are there other features of an artificial tear you deem important for this patient group?

Margie Recalde
Ideally, an artificial tear would last throughout the day and not cause irritation upon instillation as, in general, products that feel comfortable are more likely to be used consistently.

LACRISERT: PATIENT TYPES

Paul Karpecki
Let's turn to LACRISERT specifically, beginning with the types of patients for whom you tend to prescribe LACRISERT. What comes to mind to help you make that decision?

Margie Recalde
Some of my patients with moderate to severe DED may use LACRISERT exclusively, while for others it is adjunctive to other therapies. Every patient is different, and one important consideration is whether a patient can adhere to a three- or four-times daily artificial tear regimen in addition to the other drops and/or oral medications they may already be on. I always consider LACRISERT for patients with moderate to severe DED who have trouble using artificial tears. Because of its sustained residence time on the ocular surface, it can also be another nighttime option to consider for patients with lagophthalmos and exposure keratitis.

Derek Cunningham
I agree. Patients who have intense DED symptoms first thing in the morning are excellent candidates for nighttime LACRISERT. Historically, I think LACRISERT has been used as a last resort choice, after other treatments have failed. But from my experience, reserving LACRISERT for end-stage disease puts patients at a disadvantage: with insufficient tear fluid to help the insert dissolve, those with very severe DED may experience greater discomfort or foreign body sensation with the insert. Now, I tend to prescribe LACRISERT for younger patients with moderate disease rather than reserving it for a later stage.

Douglas Devries
I've tried LACRISERT in patients with moderate to severe DED of different etiologies, and have found it most useful in those who can't use artificial tears as often as they'd like. These patients often have significant punctate epithelial keratitis (PEK) **(Figure 1)**. These patients, who may have already experienced some decreased vision related to corneal epithelial damage, tend to find relief with LACRISERT and tolerate the transient blurred vision that may occur. My decision to prescribe LACRISERT is typically based on disease severity rather than subtype.

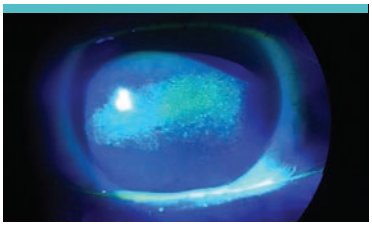


Figure 1. *Central PEK revealed by fluorescein staining in a patient with severe DED (image courtesy of Margie Recalde, OD).*

Paul Karpecki
Another important moderate to severe DED patient group to consider is contact lens wearers, who already have the dexterity needed to place the insert into the inferior cul-de-sac.

Douglas Devries
Certainly, and in any case, I would suggest giving appropriate patients with moderate to severe DED a trial of LACRISERT therapy whenever possible. This gives patients a chance to assess whether the insert will provide relief and be compatible with their lifestyle.

Paul Karpecki
Research has also shown that patients with moderate to severe DED and a history of cataract or refractive surgery experienced significant improvement in DED symptoms following treatment with LACRISERT.[8] What has been your experience with these patient populations?

Derek Cunningham
In my experience, LACRISERT works well in patients who have had cataract or LASIK surgery. These patients may have some degree of corneal neuropathy and lack the neurostimulation to produce the tear volume that they need.

Paul Karpecki
I agree, and in fact, some patients undergoing refractive surgeries are driven by convenience and looking for freedom from spectacles, contact lenses, solutions, etc. LACRISERT may be a good option for post-refractive surgery patients with moderate to severe DED for whom the idea of putting drops in every few hours may be especially unappealing.

LACRISERT: PLACE IN THERAPY

Paul Karpecki
Where do you see LACRISERT fitting within the increasingly crowded DED treatment landscape? How does it work with the other technologies?

INDICATIONS AND USAGE

LACRISERT is indicated in patients with moderate to severe dry eye syndromes, including keratoconjunctivitis sicca. LACRISERT is indicated especially in patients who remain symptomatic after an adequate trial of therapy with artificial tear solutions. LACRISERT is also indicated for patients with exposure keratitis, decreased corneal sensitivity, and recurrent corneal erosions.

IMPORTANT SAFETY INFORMATION

- LACRISERT is contraindicated in patients who are hypersensitive to hydroxypropyl cellulose.
- Instructions for inserting and removing LACRISERT should be carefully followed.
- If improperly placed, LACRISERT may result in corneal abrasion. Because LACRISERT may cause transient blurred vision, patients should be instructed to exercise caution when driving or operating machinery.
- The following adverse reactions have been reported, but were in most instances mild and temporary: transient blurring of vision, ocular discomfort or irritation, matting or stickiness of eyelashes, photophobia, hypersensitivity, eyelid edema, and hyperemia.

Please see full Prescribing Information for LACRISERT® on page 4.

Derek Cunningham
I view LACRISERT as complementary to many other treatment modalities for moderate to severe DED. When we decide to use LACRISERT, we're usually making an addition, not a substitution.

> *"To utilize LACRISERT more effectively, clinicians first need to be aware that it is an option for patients not only with more advanced disease but also with key moderate to severe DED subtypes such as contact lens wearers, those with lagophthalmos, and patients who have had cataract or LASIK surgery."*

Margie Recalde
I agree that it is complementary to therapies that address the underlying causes of DED. Patients with moderate to severe DED may need both targeted DED therapies and lubrication from LACRISERT. In my experience, whether it is used alone or adjunctively, treatment with LACRISERT usually results in a noticeable improvement in symptoms as well as clinical signs such as corneal staining.

Douglas Devries
Education is also a critical component of therapy with LACRISERT—it helps patients understand what to expect and overcome frustration. I like to use the analogy of an IV drip to explain the continuous release of LACRISERT when counseling patients.

Derek Cunningham
As with any prescription, letting patients know about side effects they may experience, such as blurred vision, helps manage their expectations and reduces the likelihood that they will be alarmed or upset should side effects occur.

> *"It's time to reconsider this unique artificial tear insert for our patients with moderate to severe DED."*

LOOKING AHEAD

Paul Karpecki
There exists a considerable body of research on LACRISERT. What do you feel are knowledge gaps about the product?

Douglas Devries
One of the biggest gaps is awareness—LACRISERT is often not included in DED treatment algorithms. There's clearly a need to communicate where in the DED treatment landscape LACRISERT can be useful.

Margie Recalde
Yes. LACRISERT was first introduced almost 30 years ago, long before the advent of other prescription treatments for moderate to severe DED. To utilize LACRISERT more effectively, clinicians first need to be aware that it is an option for patients not only with more advanced disease but also with key moderate to severe DED subtypes such as contact lens wearers, those with lagophthalmos, and patients who have had cataract or LASIK surgery.

Derek Cunningham
It's easy to forget about a technology that has been around for decades, but the fact remains that LACRISERT is among the very few prescription treatments specifically approved for moderate to severe DED in the US. Furthermore, LACRISERT was introduced at a time when the science of DED pathophysiology was not as advanced as is today; now, there should be greater recognition of the utility of LACRISERT as an adjunct to other DED treatments that address different aspects of this complex, multifactorial disease. When integrating LACRISERT into a DED treatment algorithm, eyecare practitioners may consider using it for moderate disease first—ie, don't wait to use it only on extremely severe or recalcitrant cases—and as an adjunct to other DED therapies, especially for patients who feel the need to use artificial tears multiple times per day.

Margie Recalde
I agree. With the advent of newer treatments for DED, I think we've downplayed the importance of artificial tears. While artificial tears alone may not suffice for some patients, they remain an essential part of DED therapeutic regimens, and for many patients, LACRISERT may be a better option than conventional drops.

Paul Karpecki
In the past, the chance of success with any DED therapy was limited because of a lack of knowledge about DED and few treatment options for such elements as inflammation. Today, the opportunity for LACRISERT is greater thanks to a better understanding of the disease, and that is why it's time to reconsider this unique artificial tear insert for our patients with moderate to severe DED.

Introducing LACRISERT to Patients: Application Tips

- **Make sure hands are clean when putting the insert in**
- **Use good lighting and a mirror**
- **If the insert becomes dislodged, take it out and put another one in**
- **Some patients may benefit from the following suggestions:**
  - » Contact lens wearers should put lenses in first, then place LACRISERT
  - » Makeup wearers should apply makeup first, then place LACRISERT
  - » Use gentle pressure when picking up the insert with the applicator
  - » Apply a preservative-free artificial tear prior to inserting LACRISERT if necessary to help the insert dissolve[9]
  - » LACRISERT may be used at night or in the morning [9]

REFERENCES
1. J1. Jones L, Downie LE, Korb D, et al. TFOS DEWS II management and therapy report. *Ocul Surf*. 2017;15(3):575-628. **2.** Trattler WB, Majmudar PA, Donnenfeld ED, McDonald MB, Stonecipher KG, Goldberg DF. The Prospective Health Assessment of Cataract Patients' Ocular Surface (PHACO) study: the effect of dry eye. *Clin Ophthalmol*. 2017;11:1423-30. **3.** Nichols JJ, Ziegler C, Mitchell GL, Nichols KK. Self-reported dry eye disease across refractive modalities. *Invest Ophthalmol Vis Sci*. 2005;46(6):1911-4. **4.** Gibbons A, Ali TK, Waren DP, Donaldson KE. Causes and correction of dissatisfaction after implantation of presbyopia-correcting intraocular lenses. *Clin Ophthalmol*. 2016;10:1965-70. **5.** Levinson BA , Rapuano CJ, Cohen EJ, Hammersmith KM, Ayres BC, Laibson PR. Referrals to the Wills Eye Institute Cornea Service after laser in situ keratomileusis: reasons for patient dissatisfaction. *J Cataract Refract Surg*. 2008;34(1):32-9. **6.** Bron AJ, de Paiva CS, Chauhan SK, et al. TFOS DEWS II pathophysiology report. *Ocul Surf*. 2017;15(3):438-510. **7.** Craig JP, Nichols KK, Akpek EK, et al. TFOS DEWS II definition and classification report. *Ocul Surf*. 2017;15(3):276-283. **8.** Luchs JI, Nelinson DS, Macy JI, for the LAC-07-01 Study Group. Efficacy of hydroxypropyl cellulose ophthalmic inserts (LACRISERT) in subsets of patients with dry eye syndrome: findings from a patient registry. *Cornea*. 2010;29(12):1417-27. **9.** Lamberts DW, Langston DP, Chu W. A clinical study of slow-releasing artificial tears. *Ophthalmology*. 1978;85(8):794-800.

BAUSCH + LOMB

STERILE OPHTHALMIC INSERT

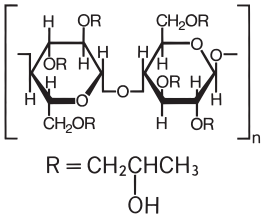
LACRISERT®

(hydroxypropyl cellulose ophthalmic insert)

DESCRIPTION

LACRISERT® (hydroxypropyl cellulose ophthalmic insert) is a sterile, translucent, rod-shaped, water soluble, ophthalmic insert made of hydroxypropyl cellulose, for administration into the inferior cul-de-sac of the eye.

The chemical name for hydroxypropyl cellulose is cellulose, 2-hydroxypropyl ether. It is an ether of cellulose in which hydroxypropyl groups (-$CH_2CHOHCH_3$) are attached to the hydroxyls present in the anhydroglucose rings of cellulose by ether linkages. A representative structure of the monomer is:



$$R = CH_2CHCH_3 \quad (OH)$$

The molecular weight is typically 1×10^6.

Hydroxypropyl cellulose is an off-white, odorless, tasteless powder. It is soluble in water below 38°C, and in many polar organic solvents such as ethanol, propylene glycol, dioxane, methanol, isopropyl alcohol (95%), dimethyl sulfoxide, and dimethyl formamide.

Each LACRISERT is 5 mg of hydroxypropyl cellulose. LACRISERT contains no preservatives or other ingredients. It is about 1.27 mm in diameter by about 3.5 mm long.

LACRISERT is supplied in packages of 60 units, together with illustrated instructions and a special applicator for removing LACRISERT from the unit dose blister and inserting it into the eye. A spare applicator is included in each package.

CLINICAL PHARMACOLOGY

Pharmacodynamics

LACRISERT acts to stabilize and thicken the precorneal tear film and prolong the tear film breakup time which is usually accelerated in patients with dry eye states. LACRISERT also acts to lubricate and protect the eye.

LACRISERT usually reduces the signs and symptoms resulting from moderate to severe dry eye syndromes, such as conjunctival hyperemia, corneal and conjunctival staining with rose bengal, exudation, itching, burning, foreign body sensation, smarting, photophobia, dryness and blurred or cloudy vision. Progressive visual deterioration which occurs in some patients may be retarded, halted, or sometimes reversed.

In a multicenter crossover study the 5 mg LACRISERT administered once a day during the waking hours was compared to artificial tears used four or more times daily. There was a prolongation of tear film breakup time and a decrease in foreign body sensation associated with dry eye syndrome in patients during treatment with inserts as compared to artificial tears; these findings were statistically significantly different between the treatment groups. Improvement, as measured by amelioration of symptoms, by slit lamp examination and by rose bengal staining of the cornea and conjunctiva, was greater in most patients with moderate to severe symptoms during treatment with LACRISERT. Patient comfort was usually better with LACRISERT than with artificial tears solution, and most patients preferred LACRISERT.

In most patients treated with LACRISERT for over one year, improvement was observed as evidenced by amelioration of symptoms generally associated with keratoconjunctivitis sicca such as burning, tearing, foreign body sensation, itching, photophobia and blurred or cloudy vision.

During studies in healthy volunteers, a thickened precorneal tear film was usually observed through the slit-lamp while LACRISERT was present in the conjunctival sac.

Pharmacokinetics and Metabolism

Hydroxypropyl cellulose is a physiologically inert substance. In a study of rats fed hydroxypropyl cellulose or unmodified cellulose at levels up to 5% of their diet, it was found that the two were biologically equivalent in that neither was metabolized.

Studies conducted in rats fed ^{14}C-labeled hydroxypropyl cellulose demonstrated that when orally administered, hydroxypropyl cellulose is not absorbed from the gastrointestinal tract and is quantitatively excreted in the feces.

Dissolution studies in rabbits showed that hydroxypropyl cellulose inserts became softer within 1 hour after they were placed in the conjunctival sac. Most of the inserts dissolved completely in 14 to 18 hours; with a single exception, all had disappeared by 24 hours after insertion. Similar dissolution of the inserts was observed during prolonged administration (up to 54 weeks).

INDICATIONS AND USAGE

LACRISERT is indicated in patients with moderate to severe dry eye syndromes, including keratoconjunctivitis sicca. LACRISERT is indicated especially in patients who remain symptomatic after an adequate trial of therapy with artificial tear solutions.

LACRISERT is also indicated for patients with:

- Exposure keratitis
- Decreased corneal sensitivity
- Recurrent corneal erosions

CONTRAINDICATIONS

LACRISERT is contraindicated in patients who are hypersensitive to hydroxypropyl cellulose.

WARNINGS

Instructions for inserting and removing LACRISERT should be carefully followed.

PRECAUTIONS

General

If improperly placed, LACRISERT may result in corneal abrasion (see DOSAGE AND ADMINISTRATION).

Information for Patients

Patients should be advised to follow the instructions for using LACRISERT which accompany the package.

Because this product may produce transient blurring of vision, patients should be instructed to exercise caution when operating hazardous machinery or driving a motor vehicle.

Drug Interactions

Application of hydroxypropyl cellulose ophthalmic inserts to the eyes of unanesthetized rabbits immediately prior to or two hours before instilling pilocarpine, proparacaine HCl (0.5%), or phenylephrine (5%) did not markedly alter the magnitude and/or duration of the miotic, local corneal anesthetic, or mydriatic activity, respectively, of these agents. Under various treatment schedules, the anti-inflammatory effect of ocularly instilled dexamethasone (0.1%) in unanesthetized rabbits with primary uveitis was not affected by the presence of hydroxypropyl cellulose inserts.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Feeding of hydroxypropyl cellulose to rats at levels up to 5% of their diet produced no gross or histopathologic changes or other deleterious effects.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

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

ADVERSE REACTIONS

The following adverse reactions have been reported in patients treated with LACRISERT, but were in most instances mild and transient:

- Transient blurring of vision (See PRECAUTIONS)
- Ocular discomfort or irritation
- Matting or stickiness of eyelashes
- Photophobia
- Hypersensitivity
- Edema of the eyelids
- Hyperemia

To report SUSPECTED ADVERSE REACTIONS, contact Bausch + Lomb, a division of Valeant Pharmaceuticals North America LLC at 1-800-321-4576 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DOSAGE AND ADMINISTRATION

One LACRISERT ophthalmic insert in each eye once daily is usually sufficient to relieve the symptoms associated with moderate to severe dry eye syndromes.

Individual patients may require more flexibility in the use of LACRISERT; some patients may require twice daily use for optimal results.

Clinical experience with LACRISERT indicates that in some patients several weeks may be required before satisfactory improvement of symptoms is achieved.

LACRISERT is inserted into the inferior cul-de-sac of the eye beneath the base of the tarsus, not in apposition to the cornea, nor beneath the eyelid at the level of the tarsal plate. If not properly positioned, it will be expelled into the interpalpebral fissure, and may cause symptoms of a foreign body. Illustrated instructions are included in each package. While in the licensed practitioner's office, the patient should read the instructions, then practice insertion and removal of LACRISERT until proficiency is achieved.

NOTE: Occasionally LACRISERT is inadvertently expelled from the eye, especially in patients with shallow conjunctival fornices. The patient should be cautioned against rubbing the eye(s) containing LACRISERT, especially upon awakening, so as not to dislodge or expel the insert. If required, another LACRISERT ophthalmic insert may be inserted. If experience indicates that transient blurred vision develops in an individual patient, the patient may want to remove LACRISERT a few hours after insertion to avoid this. Another LACRISERT ophthalmic insert maybe inserted if needed.

If LACRISERT causes worsening of symptoms, the patient should be instructed to inspect the conjunctival sac to make certain LACRISERT is in the proper location, deep in the inferior cul-de-sac of the eye beneath the base of the tarsus. If these symptoms persist, LACRISERT should be removed and the patient should contact the practitioner.

HOW SUPPLIED

LACRISERT, a sterile, translucent, rod-shaped, water-soluble, ophthalmic insert made of hydroxypropyl cellulose, 5 mg, is supplied as follows:

NDC 24208-800-60 in packages containing 60 unit doses (each wrapped in an aluminum blister), two reusable applicators, and a plastic storage container to store the applicators after use.

Storage

Store below 30°C (86°F)

Distributed by:
Bausch + Lomb, a division of
Valeant Pharmaceuticals North America LLC
Bridgewater, NJ 08807 USA

Manufactured by:
Renaissance Lakewood, LLC
Lakewood, NJ 08701 USA

9421404

Rev. 09/16

REF-LAC-0118