LACRISERT®
(hydroxypropyl cellulose ophthalmic insert)

LACRISERT® (hydroxypropyl cellulose ophthalmic insert) in Current Practice: Reflections on A Longstanding Therapy for Moderate to Severe Dry Eye

A Roundtable Discussion held July 30th, 2019

PARTICIPANTS:

Participants are paid consultants of Bausch + Lomb

Preeya Gupta, MD
is clinical medical director of Duke Eye Center and an associate professor of ophthalmology at Duke University Eye Center in Durham, NC.

William Trattler, MD
practices at the Center for Excellence in Eye Care in Miami, FL.

Brett Levinson, MD
practices at Specialized Eye Care in Baltimore, MD.

Audrey Talley Rostov, MD
***Moderator**, is a partner at Northwest Eye Surgeons in Seattle, WA.*

INTRODUCTION

The past decade has seen substantial growth in the number of treatment options for dry eye disease (DED), with therapies available to address several aspects of this multifactorial disease, including meibomian gland dysfunction (MGD), tear insufficiency, and the ocular surface inflammation at the root of DED's cyclic disease process.[1]

Tear supplementation has long been a foundational therapeutic strategy in DED, and a wide variety of products exists. LACRISERT, a water soluble, preservative-free, slow-release lubricant indicated for patients with moderate to severe DED, has been available for decades. There is a great deal of evidence in the literature that LACRISERT can increase tear film stability, protect the ocular surface, and improve symptoms.[2-5] However, the insert remains underused in practice as new treatment modalities for DED continue to emerge.

A panel of experts was convened to discuss the role of LACRISERT in moderate to severe DED, characterize patient types in whom LACRISERT tends to be effective, and share practical suggestions from their experience with LACRISERT.

DED DIAGNOSIS AND STAGING

Audrey Talley Rostov
We all see a large number of patients with DED. What is your approach to the diagnosis and staging of DED in day-to-day practice?
In my experience, questionnaires are an easy, inexpensive tool for DED screening, and the tear osmolarity and matrix metalloproteinase-9 (MMP-9) point-of-care tests are especially helpful in identifying patients who may not report the typical symptoms of irritation and foreign body sensation. Once the diagnosis is established, DED can be classified into subtypes in various ways. In my own clinic, patients are categorized as mild, moderate, or severe based mainly on symptomatology and point-of-care testing.

Brett Levinson
To me, history-taking is most important in diagnosing DED, and I prefer asking targeted questions about symptoms (including blurry vision, crusty eyelids, and the feeling of tired eyes) in person, rather than using questionnaires. After taking the history, it is important to perform a careful examination of the eyelids and face, nose, and malar region for rosacea. In many cases, a combination of history, exam findings, and tear breakup time (TBUT) is sufficient to lead to a diagnosis.

Audrey Talley Rostov
I find that questionnaires help keep my patients occupied in the waiting room and give them an opportunity to start thinking about their symptoms. Clinical examination is a main source of information, of course, but I also like point-of-care testing with tear osmolarity and MMP-9 because they produce numeric values that can be used to help patients see changes with treatment.

Preeya Gupta
The formality and sheer amount of information conveyed by many DED staging criteria can be intimidating, probably more so for less experienced clinicians.[6,7] I find it can be simpler to look at disease severity and available treatment options from a clinical perspective, looking at degree of symptoms, point-of-care test results, and physical examination findings.

Brett Levinson
In my practice, patients with DED are categorized as mild, moderate, and severe, and just as we use symptoms—not objective findings—as the key clinical indicator for cataract surgery, I place more importance on how debilitating symptoms are than on signs in determining DED severity.

Audrey Talley Rostov
Symptoms are absolutely important to consider—and patients experiencing more severe symptoms are likelier to be motivated to adhere to treatment. Similar to our approach to glaucoma therapy, it is important to have a treatment paradigm and at least some type of staging system for DED, even if this varies from practitioner to practitioner.

Brett Levinson
Glaucoma is an excellent analogy. Just as we would not wait to see visual field loss to treat a patient with elevated intraocular pressure (IOP) and optic nerve cupping, we should not wait for certain signs such as superficial punctate keratitis to diagnose or treat DED. If the patient is symptomatic, we need to address the symptoms aggressively.

TEAR SUPPLEMENTATION

Audrey Talley Rostov
What is the importance of tear supplementation in managing moderate to severe DED?

William Trattler
Artificial tears have a disease-modifying role beyond symptom relief in DED, even though they may not directly address the underlying inflammatory cause of DED.[7] In clinical trials, patients on artificial tears consistently demonstrate improvement in a variety of DED signs and symptoms.[8]

Audrey Talley Rostov
Further, artificial tears can help simply by diluting the tears and reducing the inflammatory load on the ocular surface. I use preservative-free products whenever possible,

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

especially in cases of moderate to severe DED.

Preeya Gupta
Artificial tears are a foundational therapy for DED, and many patients are pleased to have control over their use. At the same time, frequent dosing can be bothersome. For me, this is where a therapy like LACRISERT® (hydroxypropyl cellulose ophthalmic insert) plays a crucial role. Because of its sustained release, LACRISERT helps avoid the frustration patients with moderate to severe DED can experience with dosing of artificial tears multiple times a day.

LACRISERT: CLINICAL UTILITY

Audrey Talley Rostov
Let's talk more about LACRISERT. At what point do you consider prescribing LACRISERT? Where does it fit in the treatment landscape?

Preeya Gupta
I offer LACRISERT to patients with moderate to severe DED, and I find that many of them prefer the insert to using artificial tears. These patients tend to be among the younger age groups, who are increasingly affected by DED and less likely to have any substantial dexterity issues that would make using LACRISERT a challenge.[9]

Audrey Talley Rostov
In my practice, LACRISERT is a valuable adjunct in treating moderate to severe DED and can provide sustained relief to those who require repeated use of artificial tears throughout the day.

> *"In my practice, LACRISERT is a valuable adjunct in treating moderate to severe DED and can provide sustained relief to those who require repeated use of artificial tears throughout the day."*

William Trattler
Contact lens wearers with moderate to severe DED are another important group to consider for therapy with LACRISERT. If they have the dexterity to handle contacts, they can often be successful with LACRISERT.

Brett Levinson
I've also had success with LACRISERT in contact lens wearers, including keratoconus patients wearing custom lenses. In my experience, patients with moderate to severe DED and inferior lid malposition or inferior Salzmann's nodules also seem to do well with LACRISERT.

William Trattler
Because LACRISERT needs enough moisture on the ocular surface to start the melting process, I would consider using punctal plugs prior to LACRISERT for patients with significant tear insufficiency. When tear volume is too low to dissolve the insert, it may cause discomfort or irritation.

Preeya Gupta
Another patient population that may benefit from the once-daily dosing of LACRISERT are those with moderate to severe DED who are taking multiple topical ocular therapies. As we have learned from studies of glaucoma patients, treatment adherence tends to diminish as the number of drops per day increases.[10]

Audrey Talley Rostov
I agree, and I've found that LACRISERT can also be helpful for patients with moderate to severe DED linked to extended screen time. As our daily usage of digital devices continues to increase, much of the population (including the younger generations) is at risk for digital eye strain and associated dry eye symptoms.[11]

Brett Levinson
In my experience, LACRISERT seems to work well in patients with moderate to severe DED and severe loss of meibomian glands. These patients may be older but respond well to LACRISERT as long as dexterity is not an issue.

Preeya Gupta
Yes, it is important to recognize that the evaporative and aqueous-deficient components of DED often coexist.[1] Addressing MGD can be a critical part of DED treatment, and so is care of low tear volume. In my experience, LACRISERT is complementary to therapies directed at MGD–they are not mutually exclusive.

> *"In an open-label, 4-week registry study, most patients treated with LACRISERT showed significant improvement in Ocular Surface Disease Index (OSDI) scores, various symptoms including discomfort, burning, dryness, grittiness, stinging, and light sensitivity, and DED signs including TBUT, fluorescein staining score, and Schirmer test".*

evaporative DED, when in fact, the vast majority of patients with DED have some degree of both conditions.[1]

William Trattler
In an open-label, 4-week registry study, most patients treated with LACRISERT showed significant improvement in Ocular Surface Disease Index (OSDI) scores, various symptoms including discomfort, burning, dryness, grittiness, stinging, and light sensitivity, and DED signs including TBUT, fluorescein staining score, and Schirmer test.[3-5] Based on subgroup analyses, the treatment benefit of LACRISERT extended to contact lens wearers and those with a history of cataract or refractive surgery **(Figure 1)**.[4]

Mean Percentage Improvement in OSDI Scores After 1 Month of LACRISERT Treatment

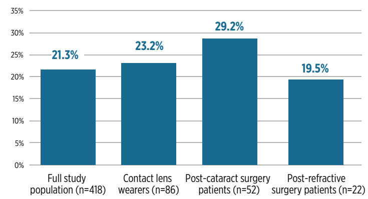

Figure 1. *Patients in a 4-week LACRISERT registry study experienced significant reductions in DED symptoms ($P < 0.05$) as measured by the OSDI survey.[4] Though a registry study does not provide the same level of evidence as a prospective, controlled trial, it does offer the opportunity to evaluate patients in a real-world setting. In this study, patients were allowed to continue with existing DED therapies, so changes in symptoms with LACRISERT could have been influenced by concomitant treatments.*

Audrey Talley Rostov
Excellent point. We have discussed contact lens wearers, but for surgical candidates with preexisting moderate to severe DED, what has been your experience treating with LACRISERT?

William Trattler
I haven't used LACRISERT preoperatively or immediately after laser vision correction, but I've certainly found it helpful in patients with moderate to severe DED and a history of cataract or refractive surgery.

Brett Levinson
Patients with concomitant glaucoma and moderate to severe DED may particularly benefit from LACRISERT therapy, as DED in these patients is often exacerbated by excessive exposure to preservatives in IOP-lowering medications.[12,13]

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.

Preeya Gupta
I find that patients with glaucoma are among the most difficult DED subpopulations to treat. Besides significant symptoms, these patients can present with varying degrees of corneal hypoesthesia and disrupted ocular surface integrity, changes that are difficult to fully combat without modifying their topical glaucoma medications.[13,14]

Audrey Talley Rostov
LACRISERT® (hydroxypropyl cellulose ophthalmic insert) is also indicated for patients with decreased corneal sensitivity.[2] Where would you place LACRISERT in the treatment of those with decreased corneal sensitivity?

William Trattler
LACRISERT may have a role in treating moderate to severe DED patients with a history of prior herpes simplex virus (HSV) keratitis. Loss of corneal sensitivity is a common complication of recurrent HSV infection.[15] Such patients can be difficult to manage because although they often have extensive evidence of corneal damage, their eyes don't feel as uncomfortable due to corneal hypoesthesia.

Audrey Talley Rostov
Yes, in patients with moderate to severe DED, the relative lack of symptoms can lead to poor adherence with frequent artificial tear use. Likewise, patients with a history of corneal transplantation often have decreased corneal sensitivity.[16] LACRISERT, which provides sustained lubrication throughout the day, can have an important role in treating this patient group.

PATIENT COUNSELING NEEDS AND USAGE RECOMMENDATIONS

Audrey Talley Rostov
In counseling patients who are trying LACRISERT for the first time, what is important to emphasize? What recommendations do you have for making the process smooth and efficient?

Brett Levinson
I or one of my staff always show patients how to use LACRISERT—our experience is that when patients learn to do it themselves in the office, the adherence rate is higher. A common mistake I see patients make when placing the insert is to put it on or near the eyelid margin, so I show patients how to bury the insert deep into the inferior fornix and then how to lift the lid up and over.

Preeya Gupta
Using a magnifying mirror can help ensure that patients can see what they are doing, and positive encouragement is also important. With practice over time, patients can become more adept at using LACRISERT.

Audrey Talley Rostov
I also tell my patients to peel open the package slowly on a flat surface to prevent the insert from popping out.

Preeya Gupta
Some patients also assume that they need to force the applicator into the insert, which actually makes it more difficult for it to dislodge; demonstrating the use of gentle pressure with the applicator can help. In those with especially low tear volume, an artificial tear drop can also help the insert stay in the fornix and begin to dissolve.

William Trattler
Do you recommend insertion in the morning or the evening?

Brett Levinson
It depends on the patient. Some may prefer using the insert upon awakening. However, some patients who experience blur with LACRISERT prefer to apply the inserts when they get to work or at midday, when they begin to experience to dryness related to prolonged near work and computer use. For those whose DED symptoms are worst first thing in the morning, or for those with nocturnal lagophthalmos, I recommend using at night.

KNOWLEDGE GAPS

Audrey Talley Rostov
Where are the knowledge gaps about LACRISERT? What do people need to know?

William Trattler
There are many published studies supporting the use of LACRISERT and many positive experiences over time. The major challenge, in my view, is the lack of awareness and knowledge of the technology among clinicians, especially those just entering practice.

Preeya Gupta
More than anything, it's critical for us to keep LACRISERT in mind and offer it to any patient who is using artificial tears more than two to three times a day, has good dexterity, and is motivated to try treatment alternatives. As we strive to address all the interrelated aspects of moderate to severe DED (tear insufficiency, MGD, inflammation), it's important to remember that LACRISERT can be a complement to many of the other treatment modalities we use.

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Starting Patients Off Right With LACRISERT

- **Use samples to demonstrate LACRISERT application**
- **Make magnifying mirrors available to help patients visualize technique**
- **Ensure multiple members of the practice team are trained in coaching first-time LACRISERT users**
- **Beyond the provided instructions, some patients may benefit from the following suggestions:**
  - » Open the package on a flat surface to keep the insert from popping out
  - » 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[17]
  - » LACRISERT may be used at night or in the morning[17]

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BAUSCH + LOMB

STERILE OPHTHALMIC INSERT

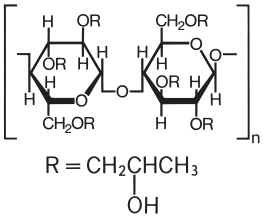
LACRISERT®

(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

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