Supplement to CRST Cataract & Refractive Surgery Today
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Tackling Ocular Inflammation and Pain

With Lotemax Gel Following Ocular Surgery

INDICATION

LOTEMAX® GEL (loteprednol etabonate ophthalmic gel) 0.5% is indicated for the treatment of post-operative inflammation and pain following ocular surgery.

IMPORTANT SAFETY INFORMATION ABOUT LOTEMAX® GEL

- LOTEMAX® GEL 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.
- Prolonged use of corticosteroids may result in glaucoma with damage to the optic nerve, defects in visual acuity and fields of vision. If this product is used for 10 days or longer, IOP should be monitored.
- Use of corticosteroids may result in posterior subcapsular cataract formation.
- Use of steroids after cataract surgery may delay healing and increase the incidence of bleb formation and occurrence of perforations in those with diseases causing corneal and scleral thinning. The initial prescription and renewal of the medication order should be made by a physician only after examination of the patient with the aid of magnification, and, where appropriate, fluorescein staining.
- Prolonged use of corticosteroids may suppress the host response and thus increase the hazard of secondary ocular infection. In acute purulent conditions, steroids may mask infection or enhance existing infection.
- Use of a corticosteroid medication in the treatment of patients with a history of herpes simplex requires great caution. Use of ocular steroids may prolong the course and exacerbate the severity of many viral infections of the eye (including herpes simplex).
- 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.
- Patients should not wear contact lenses when using LOTEMAX® GEL.
- The most common ocular adverse drug reactions reported were anterior chamber inflammation (5%), eye pain (2%) and foreign body sensation (2%).

Please see Full Prescribing Information for LOTEMAX® GEL on pages 11-12.

LOTEMAX® GEL
loteprednol etabonate
ophthalmic gel 0.5%

Tackling Ocular Inflammation and Pain With Lotemax Gel Following Ocular Surgery

Lotemax Gel (loteprednol etabonate ophthalmic gel 0.5%) is a corticosteroid indicated for the treatment of postoperative inflammation and pain following ocular surgery. The gel's mucoadhesive technology is engineered to bind to the mucin layer.[1,2] Its adaptive viscosity properties allow the gel to become a viscous liquid upon instillation to the eye.[3] There is a low incidence of blur with the product.[3] The nonsettling formulation provides a uniform dose with no shaking of contents.[4] Our expert panel is here to discuss their personal experiences with this formulation.

—Christopher E. Starr, MD, moderator

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Christopher E. Starr, MD, is associate professor of ophthalmology, director of the Refractive Surgery Service, director of ophthalmic education, and director of the Cornea, Cataract, and Refractive Surgery Fellowship at Weill Cornell Medical College in New York. He is a consultant to Bausch + Lomb. Dr. Starr may be reached at cestarr@med.cornell.edu.

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Please see additional Important Safety Information on page 1.

INFLAMMATION CONTROL

Christopher E. Starr, MD: We are fortunate to practice at a time when advances in technology and fine-tuned techniques, such as microincisions and femtosecond lasers, cause less disruption and collateral damage during ocular surgery. They are gentler on the eye. Considering these factors, is inflammation still relevant? Is it necessary to use steroids postoperatively in your practices? What strategies do you use to control pain and inflammation following ocular surgery?

Neda Shamie, MD: Despite the sophistication of our surgical techniques, ocular inflammation following cataract surgery is still a common cause of patient discomfort, delayed recovery, and reduced visual outcomes.[5] Although there are no established guidelines for preventing or reducing inflammation following ocular surgery, corticosteroids are commonly used for short-term control of ocular inflammation and are standard in my postoperative treatment regimen.

Dr. Starr: Inflammation is inevitable regardless of how precise and sophisticated our surgeries become. Inflammation is induced by the physical trauma, including disruption of the blood-aqueous barrier, which releases inflammatory mediators such as prostaglandins and leukotrienes from arachidonic acid. The more inflammation there is, the more corneal edema and photosensitivity there likely is, and the vision and comfort in the early postoperative period is not going to be as good.

Zaina Al-Mohtaseb, MD: With the improvement of ocular surgeries, there is also a much higher expectation of pain control from the patient. Patients are more involved in their care and pay out of pocket for premium procedures. They expect virtual perfection on day 1 in every scenario. The last thing they want to experience is unwanted pain, redness, discomfort, or negative visual implications. To help meet these expectations, controlling inflammation still plays an important part.

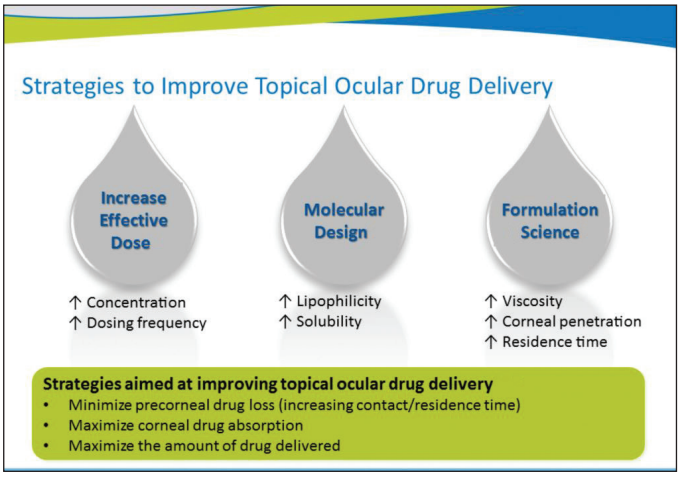

Figure 1. Drug strategies aimed at improving topical ocular drug delivery.[6-10]

Patients relate pain and inflammation to the surgery itself rather than as a byproduct after surgery.

DOSE UNIFORMITY

Dr. Starr: There are several strategies that can be used to facilitate ocular drug delivery, such as increasing the concentration or the lipophilicity, solubility, and viscosity, thereby minimizing precorneal drug loss and maximizing corneal drug absorption and the amount of drug delivered (Figure 1).[6-10]

Bausch + Lomb has made compositional and structural changes to the gel formulaton of loteprednol etabonate to provide dose uniformity.[4] In response to the ocular adverse events that may be a result of traditional steroids, the carbon-20 (C-20) ester corticosteroid was developed via retrometabolic drug design. Most ocular corticosteroids have a ketone at the C-20 position. When ocular metabolism occurs, some metabolites remain active. Loteprednol etabonate

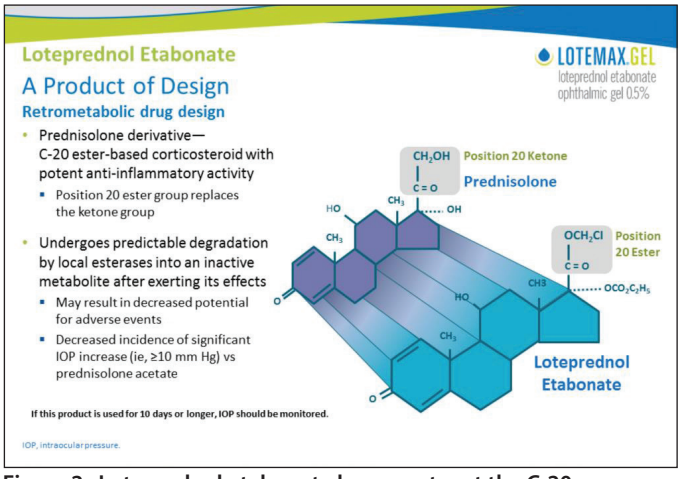

Figure 2. Loteprednol etabonate has an ester at the C-20 position.[11-13]

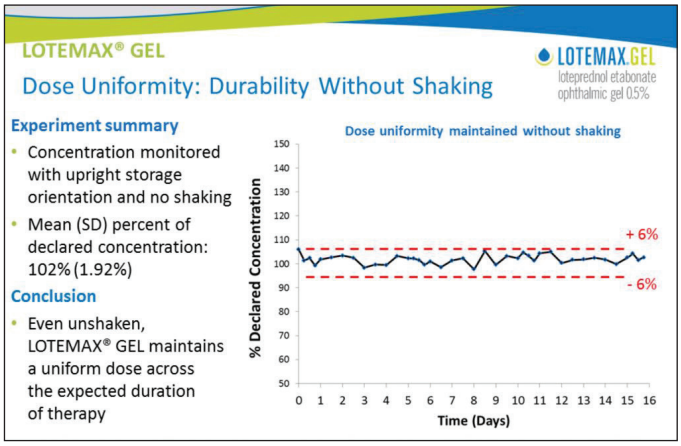

Figure 3. Even unshaken, Lotemax Gel maintains a uniform dose across the expected duration of therapy.[4,18]

has an ester at the C-20 position (Figure 2),[11-13] and ocular esterases break down the active corticosteroid into inactive metabolites. This molecular design shortens the active life of the drug. After exerting its therapeutic effects, loteprednol etabonate is converted into inactive metabolites, which may result in a lower potential for adverse events, such as increased IOP. If Lotemax Gel is used for 10 days or longer, IOP should be monitored. Multiple studies[14-16] have shown that loteprednol etabonate has an established safety profile when used to treat inflammation and pain following cataract surgery.

William B. Trattler, MD: A major problem in ocular therapeutics is the attainment of the same amount of drug at the site of action.[8] The eye has many protective barrier mechanisms that efficiently clear foreign substances as well as restrict the bioavailability of applied topical ocular agents. Following spillage, nasolacrimal drainage, tears, blinking, conjunctival and scleral absorption, and anatomical barriers, approximately 5% of the dose is actually absorbed by the cornea.[17] Any sensation of irritation causes patients to squeeze, blink, and tear, reducing retention and residence time on the ocular surface and diluting the drop. One mechanism to counteract these forces is to have a lubricating polymer that adheres to the ocular surface. Lotemax Gel contains the mucoadhesive polymer polycarbophil. What has your experience been with this formulation of Lotemax?

Dr. Al-Mohtaseb: We always have to take into account clinical studies versus real-life scenarios. Patient variability of using a product is the biggest challenge. One of the reasons I use Lotemax Gel is because it provides dose uniformity—patients do not have to shake Lotemax Gel (Figure 3).[4,18]

Drug delivery strategies are only effective when patients are compliant with the requirements, such as shaking medications before application. One study[19] found that as many as 63% of patients did not shake an ophthalmic suspension medication despite a labeled direction to shake. Lotemax Gel was not used

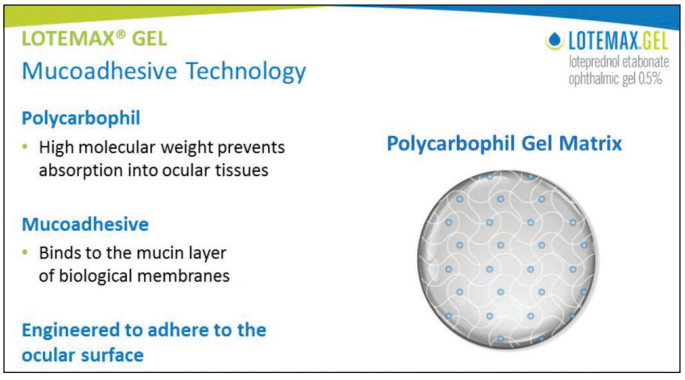

Figure 4. Lotemax Gel was engineered to adhere to the ocular surface via polycarbophil, a high molecular weight polymer.[1,2,21-23]

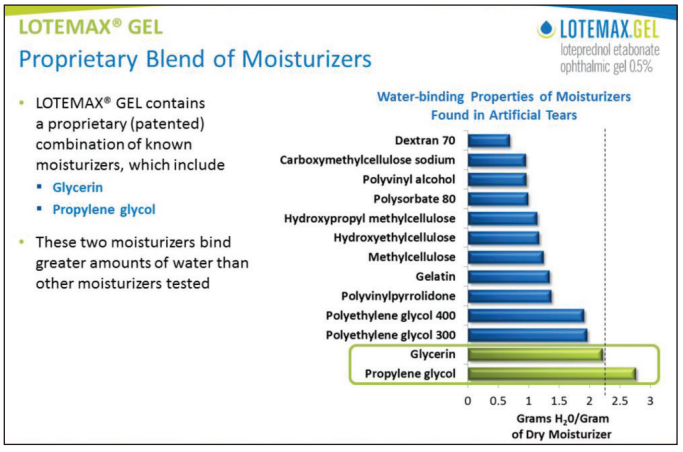

Figure 5. Lotemax Gel contains the demulcents glycerin and propylene glycol.[24]

in this study. Further, we learned from this study that subjects were very variable in their interpretation of the direction to "shake well."

Shamik Bafna, MD: With nearly two-thirds of patients not shaking the bottle at all in this study, this is significant in terms of being able to maintain the homogeneity of the drops throughout the entire cycle, from the first drop to the last drop. With Lotemax Gel, we know there is dose uniformity, because it is a gel at rest; it is nonsettling. Thus, it is not necessary to shake the drug.

Dr. Starr: Knowing the patients will have the same amount of dose in every application certainly gives me peace of mind as a surgeon. The formula of Lotemax Gel just makes sense.

Dr. Bafna: Ultimately, the goal is to get the drug into the anterior chamber to combat the inflammation and pain. Lotemax Gel was engineered to adhere to the ocular surface via polycarbophil, a high molecular weight polymer that is one of the most adherent mucoadhesives known (Figure 4).[1,2,20-23]

Dr. Shamie: The dose uniformity and adhesion properties are factors that I consider important in my decision to prescribe Lotemax Gel as it helps the patient get the same amount of drug in every drop.

FEATURES OF GEL FORMULATION

Dr. Starr: What other properties of the Lotemax formulation appeal to you?

Dr. Al-Mohtaseb: I like that the reformulation has a lower preservative concentration than its predecessor—30 ppm BAK, 70% less than the suspension formulation of loteprednol etabonate.[22]

Dr. Starr: Another formulation change with this product is the inclusion of a patented combination of moisturizers, glycerin and propylene glycol (Figure 5).[24]

Dr. Shamie: The moisturizers are a good addition. I prefer Lotemax Gel for my postoperative regimen as it is a good

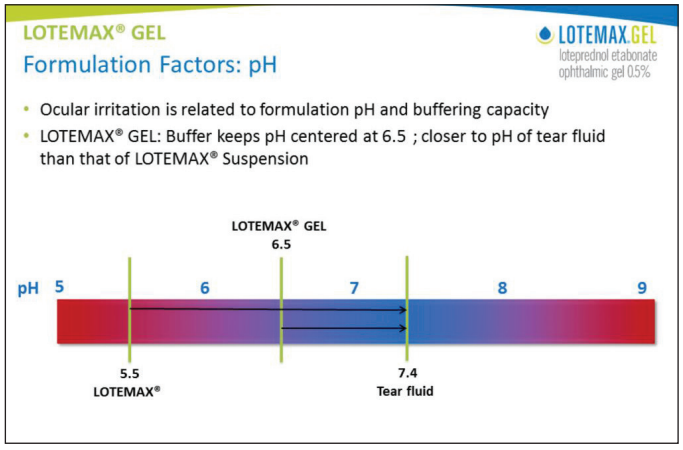

Figure 6. Lotemax Gel has a pH that is closer to the pH of tears than the suspension formulation of loteprednol etabonate.[20,22,26]

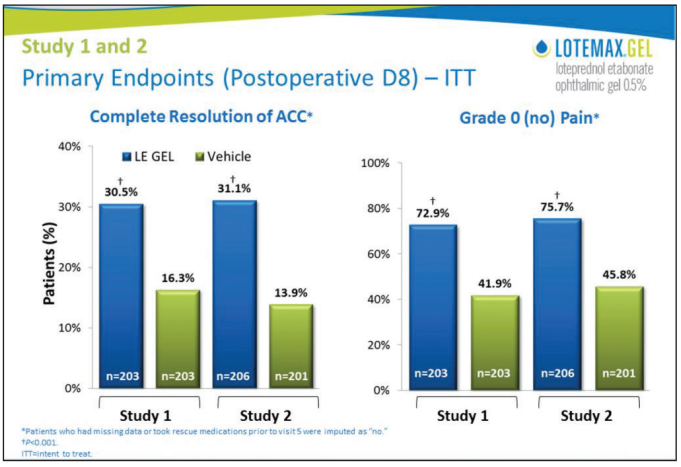

Figure 7. Compared to vehicle, significantly more Lotemax Gel-treated patients had complete resolution of anterior chamber cell and grade 0 pain at postoperative day 8.[22,25]

treatment option for helping with postoperative inflammation and pain following ocular surgery. Of course, the low incidence of IOP elevation[25] is an important added benefit for all patients.

Dr. Starr: Also, the pH in the gel, with a buffer to keep the pH centered at 6.5, is closer to the pH of tears than the suspension formulation of loteprednol etabonate (Figure 6).[20,22,26]

CLINICAL EXPERIENCE AND ADAPTIVE VISCOSITY

Dr. Starr: Let us talk about the clinical trial data for Lotemax Gel.

Dr. Trattler: The efficacy and safety profile were examined in two identical, randomized, double-masked, vehicle-controlled, parallel-group, multicenter studies.[22] In both studies, significantly more Lotemax Gel-treated patients had complete resolution of anterior chamber cell and grade 0 pain at postoperative day 8 versus vehicle—complete resolution of ACC: 30.5% vs 16.3% (study 1), 31.1% vs 13.9% (study 2) ($P<0.001$); and grade 0 pain: 72.9% vs 41.9% (study 1), 75.7% vs 45.8% (study 2) ($P<0.001$) (Figure 7).[22,25]

Dr. Bafna: What was interesting to me was that these trials went beyond looking for a little bit of inflammation to actually verifying that there were zero inflammatory cells through a slit-lamp beam. It is statistically significant that at day 8 there were higher rates of no inflammatory cells, as well as zero pain.

Also, from a formulation standpoint, although it seemed that patients might complain about blurriness upon instillation of a gel, I have not had any patients complain of blurred vision. The adaptive viscosity of Lotemax Gel allows it to be a gel at rest and a viscous liquid upon instillation (Figure 8).[3]

Dr. Starr: Yes, adaptive viscosity is an important piece of this, and it does seem counterintuitive. I have heard from some doctors who claim that it blurs, but, when I probe them and ask for evidence, I find it is usually an assumption based on the

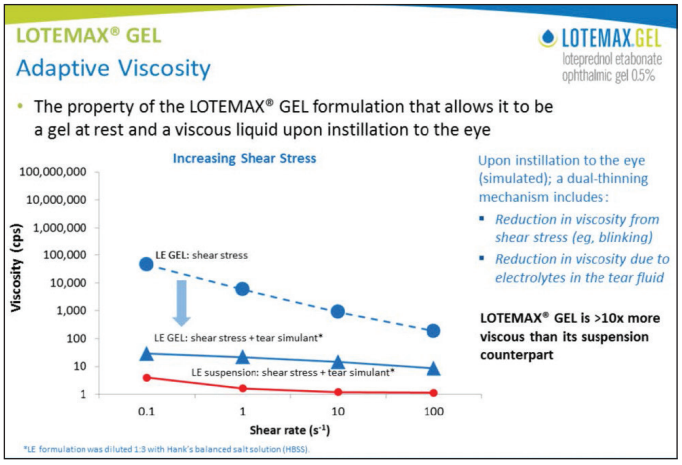

Figure 8. Lotemax Gel is a gel at rest and a viscous liquid upon instillation to the eye.[3]

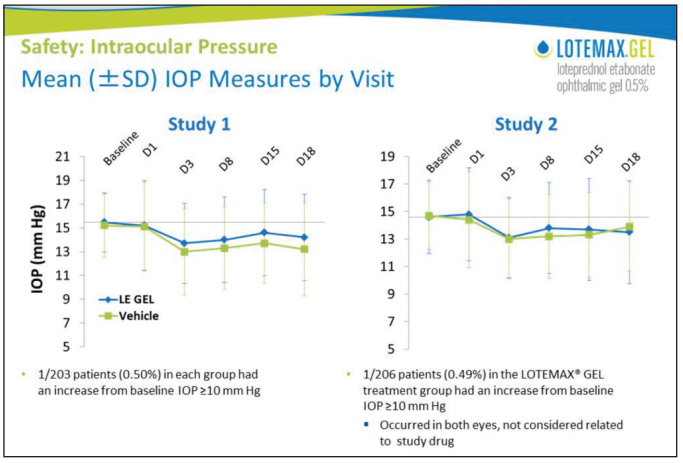

Figure 9. In phase 3 trials, the mean IOP in eyes treated with Lotemax Gel was similar to the vehicle-treated group and consistently lower than baseline. If Lotemax Gel is used for 10 days or longer, IOP should be monitored.[18,22,25]

word "gel" rather than based in patient complaints. Although it is a gel in the bottle, when it hits the eye the shear stress from blinking and the dilution with tears causes it to become much less viscous. I have not had a single complaint of blurring from patients who have been on Lotemax Gel.

Dr. Shamie: I have had patients who did not want a gel formulation. Patient education is important here. If we explain that this is indeed a gel upon instillation, but that its adaptive properties lead to its breakdown to a liquid form after blinking, then patients do not start with negative expectations.

Dr. Starr: Every drop that we put on the eye will blur temporarily; this is just a function of putting a drop on the ocular surface. It does dissipate and is certainly not of significant concern to me.

LOW INCIDENCE OF IOP ELEVATION

Dr. Starr: How have your patients tolerated Lotemax Gel, particularly with respect to IOP?

Dr. Shamie: In my experience, the majority of my patients have not reported discharge, dryness, itching, photophobia, or tearing.

Dr. Starr: Lotemax Gel has a low incidence of IOP elevation.[25] We definitely want to have a drop with a demonstrated safety profile. We all know that problems in the postoperative period can lead to pressure spikes, and the patient is not necessarily going to be aware of this increased pressure. With Lotemax Gel, there is a low incidence of elevated IOP. In phase 3 trials, the mean IOP in eyes treated with Lotemax Gel was similar to the vehicle-treated group and consistently lower than baseline (Figure 9).[18,22,25] If Lotemax Gel is used for 10 days or longer, IOP should be monitored.

Dr. Trattler: A small percentage of patients will have an elevation of pressure. However, with Lotemax Gel, there is a low

IMPORTANT SAFETY INFORMATION ABOUT LOTEMAX® GEL (CONTINUED)

- Prolonged use of corticosteroids may suppress the host response and thus increase the hazard of secondary ocular infection. In acute purulent conditions, steroids may mask infection or enhance existing infection.
- Use of a corticosteroid medication in the treatment of patients with a history of herpes simplex requires great caution. Use of ocular steroids may prolong the course and exacerbate the severity of many viral infections of the eye (including herpes simplex).
- 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.
- Patients should not wear contact lenses when using LOTEMAX® GEL.
- The most common ocular adverse drug reactions reported were anterior chamber inflammation (5%), eye pain (2%) and foreign body sensation (2%).

LOTEMAX® GEL
loteprednol etabonate
ophthalmic gel 0.5%

Please see additional Important Safety Information on page 1.

incidence of IOP spikes. With this in mind, Lotemax Gel is a good treatment option to use in patients undergoing cataract surgery who have an increased risk for elevated eye pressure spikes. It is, of course, important to point out that regardless of the structure of the steroid, it is very important to watch and monitor for pressure spikes, especially if using the drug for more than 10 days. Other risks with topical steroids should also be monitored over time.

HIGHER RISK PATIENTS

Dr. Starr: We are in agreement that Lotemax is a good treatment option to use following routine cataract surgeries. However, do you use Lotemax Gel for your higher risk patients such as white cataract, floppy iris, pseudoexfoliation, or in cases where you are expecting pupil stretching, Maylugin rings, longer cases with a higher risk of postoperative corneal swelling and inflammation.

Dr. Trattler: In my experience, Lotemax Gel definitely works well for these higher risk patients, particularly if they have glaucoma or other issues where I am worried about pressure spikes. For any of these more challenging cases, we have improved fluidics with our phaco machines, and femtosecond lasers, which in my experience makes cataract surgery easier and result in less inflammation. I monitor these patients carefully, starting on day zero, and Lotemax Gel has controlled pain and inflammation postoperatively in these patients with low occurrence of pressure spikes.

A good example is a patient who is on chronic glaucoma medication therapy. These patients tend to have a compromised ocular surface from the extended use of topical medications with preservatives. As well, these patients are at increased risk of an eye pressure spike related the use of topical steroids. I therefore prefer to use Lotemax Gel for its demonstrated efficacy profile, while being less likely to elevate eye pressure.[25] If Lotemax Gel is used for 10 days or longer, IOP should be monitored.

Dr. Shamie: I actually use Lotemax in its gel formulation far more frequently in the higher risk patients than before, especially if I am concerned about pressure spikes in complex cataract cases. Of course, I monitor them very closely. In my corneal transplant and phakic patients, I do not hesitate to use Lotemax Gel, particularly because of its low incidence of pressure elevation. With our newer lamellar corneal transplant techniques in which we target and replace only the diseased layer, we have fine-tuned our approach and in turn it causes less collateral tissue disruption. The inflammatory response is thus less aggressive. Nevertheless, Lotemax Gel is a good treatment option to treat inflammation and pain for all of our surgical patients.

Dr. Al-Mohtaseb: Being in a tertiary center, I see a large number of glaucoma patients on whom I perform Descemet's stripping automated endothelial keratoplasty, or corneal transplantation, or even cataract surgery. Lotemax Gel works well for these patients as well as the deep anterior lamellar keratoplasty patients. These are typically younger patients with keratoconus who are susceptible to developing high pressure or cataracts.

Dr. Bafna: Lotemax Gel is a good treatment option for procedures such as the Kamra corneal inlay.

Dr. Trattler: I have used Lotemax Gel in patients following pterygium surgery. It is surprising that some of these patients can get elevations in eye pressure with topical steroids. In these patients with a history of elevated eye pressure, Lotemax Gel can provide overall good results for pterygium patients, in my experience. I am diligent to monitor patients IOP carefully if Lotemax Gel is used for 10 days or longer.

Dr. Starr: With LASIK, once the flap is secure these drops are very useful in the setting of refractive laser vision correction, because Lotemax Gel has a low incidence of IOP elevation.

NO GENERIC SUBSTITUTION

Dr. Starr: There is currently no generic equivalent to the branded Lotemax Gel. How do you make sure that your patients receive the branded medication?

Dr. Shamie: First, we have to educate the patient by explaining the difference. I stress to patients that they will only have this procedure once. Steroids are, in most cases, prescribed as a short-term medication, and we rely on their efficacy for the treatment course. We can offer our eligible patients help though Bausch + Lomb coupons, making Lotemax Gel an affordable option for many patients. I also tell my patients to firmly hold their ground if they are told by the pharmacist that there is a generic equivalent. We need to make sure that the staff also understands the difference. Often, calls from the pharmacy are answered by the staff, and if they are not educated regarding your preferences, they may speak on your behalf and replace what you think is the best drop for the patient.

Dr. Starr: I am not happy when a pharmacist tries to switch my patients to a generic drop, because there is no generic equivalent. If I write Lotemax Gel, I expect patients to get Lotemax Gel. This is where medical-legal issues may come into play, because I have not educated patients on generic products that may be used, which means they may take them incorrectly. Another point of clarification is that Lotemax Gel may get confused with the older formulation of Lotemax. It is important to write Lotemax Gel on the prescription, or the patients might get the original Lotemax.

Thank you all for your time and input. I believe Lotemax Gel is a sophisticated, well-designed formulation.

1. Jasti B, Li X, Cleary G. Recent advances in mucoadhesive drug delivery systems. *Business Briefing: PharmaTech*. 2003; 194-196.
2. Bowman LM, Si E, Pang J, Archibald R, Friedlaender M. Development of a topical polymeric mucoadhesive ocular delivery system for azithromycin. *J Ocul Pharmacol Ther*. 2009;25(2):133-139.
3. Coffey MJ, DeCory HH, Lane SS. Development of a non-settling gel formulation of 0.5% loteprednol etabonate for anti-inflammatory use as an ophthalmic drop. *Clin Ophthalmol*. 2013;7:299-312.
4. Marlowe ZT, Davio SR. Dose uniformity of loteprednol etabonate ophthalmic gel (0.5%) compared with branded and generic prednisolone acetate ophthalmic suspension (1%). *Clin Ophthalmol*. 2014;8:23--29.
5. El-Harazi SM, Feldman RM. Control of intra-ocular inflammation associated with cataract surgery. *Curr Opin Ophthalmol*. 2001;12:4-8.
6. Ghate D, Edelhauser HF. Ocular drug delivery. *Expert Opin Drug Deliv*. 2006;3(2):275-287.
7. Shirasaki Y. Molecular design for enhancement of ocular penetration. *J Pharm Sci*. 2008;97(7):2462-2496.
8. Kaur IP, Kanwar M. Ocular preparations: the formulation approach. *Drug Dev Ind Pharm*. 2002;28(5):473-493.
9. Barar J, Javadzadeh AR, Omidi Y. Ocular novel drug delivery: impacts of membranes and barriers. *Expert Opin Drug Deliv*. 2008;5(5):567-581.
10. Diestelhorst M, Kwon KA, Suverkrup R. Dose uniformity of ophthalmic suspensions. *J Cataract Refract Surg*. 1998;24(5):672-677.
11. Bodor N, Buchwald P. Ophthalmic drug design based on the metabolic activity of the eye: soft drugs and chemical delivery systems. *AAPS J*. 2005;7(4):E820-E833.
12. Novack GD, Howes J, Crockett RS, Sherwood MB. Change in intraocular pressure during long-term use of loteprednol etabonate. *J Glaucoma*. 1998;7(4):266-269.
13. Bartlett JD, Horwitz B, Laibovitz R, Howes JF. Intraocular pressure response to loteprednol etabonate in known steroid responders. *J Ocul Pharmacol*. 1993;9(2):157-165.
14. Beehler C. A double-masked, placebo-controlled evaluation of 0.5% loteprednol etabonate in the treatment of postoperative inflammation. Loteprednol Etabonate Postoperative Inflammation Study Group 2. *Ophthalmology*. 1998;105:1780-1786.
15. Stewart R, Horwitz B, Howes J, et al. Double-masked, placebo-controlled evaluation of loteprednol etabonate 0.5% for postoperative inflammation. Loteprednol Etabonate Post-operative Inflammation Study Group 1. *J Cataract Refract Surg*. 1998;24:1480-1489.
16. Pflugfelder SC, Maskin SL, Anderson B, et al. A randomized, double-masked, placebo-controlled, multicenter comparison of loteprednol etabonate ophthalmic suspension, 0.5%, and placebo for treatment of keratoconjunctivitis sicca in patients with delayed tear clearance. *Am J Ophthalmol*. 2004;138:444-457.
17. Gaudana R, Ananthula HK, Parenky A, Mitra AK. Ocular drug delivery. *AAPS J*. 2010;12(3):348-360.
18. Data on file. Bausch & Lomb Incorporated.
19. Apt L, Henrick A, Silverman LM. Patient compliance with use of topical ophthalmic corticosteroid suspensions. *Am J Ophthalmol*. 1979;87(2):210-214.
20. Ali Y, Lehmussaari K. Industrial perspective in ocular drug delivery. *Adv Drug Deliv Rev*. 2006;58(11):1258-1268.
21. Lotemax Gel [package insert]. Tampa, FL: Bausch & Lomb Incorporated; September 2012.
22. Fong R, Leitritz M, Siou-Mermet R, Erb T. Loteprednol etabonate gel 0.5% for postoperative pain and inflammation after cataract surgery: results of a multicenter trial. *Clin Ophthalmol*. 2012;6:1113-1124.
23. Shaikh R, Raj Singh TR, Garland MJ, Woolfson AD, Donnelly RF. Mucoadhesive drug delivery systems. *J Pharm Bioallied Sci*. 2011;3(1):89-100.
24. Denick J, Hu Z, inventors; Bausch & Lomb Incorporated, assignee. Ophthalmic compositions including glycerin and propylene glycol. US patent 5,800,807. September 1, 1998.
25. Rajpal RK, Fong R, Comstock TL. Loteprednol etabonate ophthalmic gel 0.5% following cataract surgery: integrated analysis of two clinical studies. *Adv Ther*. 2013;30:907-923.
26. Lentner C. Geigy scientific tables. CIBA-Geigy; 1981:178-184.

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LOTEMAX®

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ophthalmic gel 0.5%

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use LOTEMAX® (loteprednol etabonate ophthalmic gel) 0.5% safely and effectively. See full prescribing information for LOTEMAX®.

LOTEMAX® (loteprednol etabonate ophthalmic gel) 0.5%
Initial U.S. Approval: 1998

----------INDICATIONS AND USAGE----------

LOTEMAX is a corticosteroid indicated for the treatment of post-operative inflammation and pain following ocular surgery. (1)

---------- DOSAGE AND ADMINISTRATION ----------

Invert closed bottle and shake once to fill tip before instilling drops.
Apply one to two drops of LOTEMAX into the conjunctival sac of the affected eye four times daily beginning the day after surgery and continuing throughout the first 2 weeks of the post-operative period. (2)

---------- DOSAGE FORMS AND STRENGTHS ----------

LOTEMAX contains 5 mg/g of loteprednol etabonate, as a sterile preserved ophthalmic gel. (3)

---------- CONTRAINDICATIONS ----------

LOTEMAX, 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. (4)

---------- WARNINGS AND PRECAUTIONS----------

- Intraocular pressure (IOP) increase – Prolonged use of corticosteroids may result in glaucoma with damage to the optic nerve, defects in visual acuity and fields of vision. If this product is used for 10 days or longer, IOP should be monitored. (5.1)
- Cataracts – Use of corticosteroids may result in posterior subcapsular cataract formation. (5.2)
- Delayed healing – The use of steroids after cataract surgery may delay healing and increase the incidence of bleb formation. In those diseases causing thinning of the cornea or sclera, perforations have been known to occur with the use of topical steroids. The initial prescription and renewal of the medication order 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. (5.3)
- Bacterial infections – Prolonged use of corticosteroids may suppress the host response and thus increase the hazard of secondary ocular infection. In acute purulent conditions, steroids may mask infection or enhance existing infection. (5.4)
- Viral infections – Employment of a corticosteroid medication in the treatment of patients with a history of herpes simplex requires great caution. Use of ocular steroids may prolong the course and may exacerbate the severity of many viral infections of the eye (including herpes simplex). (5.5)
- Fungal infections – 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. (5.6)

---------- ADVERSE REACTIONS----------

The most common adverse drug reactions were anterior chamber inflammation (5%), eye pain (2%), and foreign body sensation (2%). (6)

To report SUSPECTED ADVERSE REACTIONS, contact Bausch & Lomb at 1-800-323-0000 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch
See 17 for PATIENT COUNSELING INFORMATION

Revised: 9/2012

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

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5 WARNINGS AND PRECAUTIONS

5.1 Intraocular Pressure (IOP) Increase

Prolonged use of corticosteroids may result in glaucoma with damage to the optic nerve, defects in visual acuity and fields of vision. Steroids should be used with caution in the presence of glaucoma. If this product is used for 10 days or longer, intraocular pressure should be monitored.

5.2 Cataracts

Use of corticosteroids may result in posterior subcapsular cataract formation.

5.3 Delayed Healing

The use of steroids after cataract surgery may delay healing and increase the incidence of bleb formation. In those diseases causing thinning of the cornea or sclera, perforations have been known to occur with the use of topical steroids. The initial prescription and renewal of the medication order 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.

5.4 Bacterial Infections

Prolonged use of corticosteroids may suppress the host response and thus increase the hazard of secondary ocular infections. In acute purulent conditions of the eye, steroids may mask infection or enhance existing infection.

5.5 Viral Infections

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

5.6 Fungal Infections

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.

5.7 Contact Lens Wear

Patients should not wear contact lenses during their course of therapy with LOTEMAX.

6 ADVERSE REACTIONS

Adverse reactions associated with ophthalmic steroids include elevated intraocular pressure, which may be associated with infrequent optic nerve damage, visual acuity and field defects, posterior subcapsular cataract formation, delayed wound healing and secondary ocular infection from pathogens including herpes simplex, and perforation of the globe where there is thinning of the cornea or sclera.

The most common adverse drug reactions reported were anterior chamber inflammation (5%), eye pain (2%), and foreign body sensation (2%).

8 USE IN SPECIFIC POPULATIONS

8.1 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 (35 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 (6 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 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 (6 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. LOTEMAX should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

8.3 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 LOTEMAX is administered to a nursing woman.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

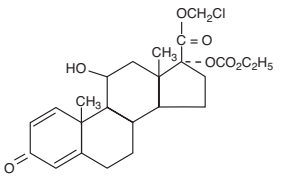
8.5 Geriatric Use

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

11 DESCRIPTION

LOTEMAX (loteprednol etabonate ophthalmic gel) 0.5% contains a sterile, topical 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-oxoandrosta-1,4-diene-17β-carboxylate

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

Each gram contains:

ACTIVE: Loteprednol Etabonate 5 mg (0.5%);

INACTIVES: Boric acid, edetate disodium dihydrate, glycerin, polycarbophil, propylene glycol, sodium chloride, tyloxapol, water for injection, and sodium hydroxide to adjust to a pH of between 6 and 7.

PRESERVATIVE: benzalkonium chloride 0.003%.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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. While glucocorticoids are known to bind to and activate the glucocorticoid receptor, the molecular mechanisms involved in glucocorticoid/glucocorticoid receptor-dependent modulation of inflammation are not clearly established. However, corticosteroids are thought to inhibit prostaglandin production through several independent mechanisms.

12.3 Pharmacokinetics

Loteprednol is lipid soluble and can penetrate 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 the inactive carboxylic acid metabolites, PJ-91 and PJ-90. The systemic exposure to loteprednol etabonate following ocular administration of LOTEMAX has not been studied in humans.

13 NONCLINICAL TOXICOLOGY

13.1 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, (600 and 300 times the maximum clinical dose, respectively) prior to and during mating did not impair fertility in either gender.

14 CLINICAL STUDIES

In two randomized, multicenter, double-masked, parallel-group, vehicle-controlled studies in 813 subjects with, post-operative inflammation, LOTEMAX was more effective compared to its vehicle in resolving anterior chamber inflammation and pain following cataract surgery. Primary endpoints were complete resolution of anterior chamber cells (cell count of 0) and no pain at post-operative day 8.

In these studies, LOTEMAX had a statistically significant higher incidence of subjects with complete clearing of anterior chamber cells (31% vs. 14-16%) and were pain free at post-operative day 8 (73-76% vs. 42-46%).

16 HOW SUPPLIED/STORAGE AND HANDLING

LOTEMAX® (loteprednol etabonate ophthalmic gel) 0.5% is a sterile ophthalmic gel supplied in a white low density polyethylene plastic bottle with a white controlled drop tip and a pink polypropylene cap in the following size:

5 g in a 10 mL bottle (NDC 24208-503-07)

Use only if imprinted neckband is intact.

Storage: Store upright at 15°-25° C (59°-77° F).

17 PATIENT COUNSELING INFORMATION

17.1 Administration

Invert closed bottle and shake once to fill tip before instilling drops.

17.2 Risk of Contamination

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

17.3 Contact Lens Wear

Patients should be advised not to wear contact lenses when using LOTEMAX.

17.4 Risk of Secondary Infection

If pain develops, redness, itching or inflammation becomes aggravated, the patient should be advised to consult a physician.

Bausch & Lomb Incorporated
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