Paul M. Karpecki, OD, FAAO

Doug Katsev, MD

Making Strides in Blepharitis Treatment

How New Insights Can Help Clinicians Elevate Patient Care

By Paul M. Karpecki, OD, FAAO; and Doug Katsev, MD

Drs. Karpecki and Katsev are paid consultants for Bausch + Lomb.

Patients suffering from blepharitis are a common, but unique, segment of eye care patients. The chronic nature of blepharitis and sometimes-confounding aspect of its diagnosis can create obstacles to treatment and management of the condition.

In recent years, the Tear Film & Ocular Surface Society Dry Eye Workshop II (DEWS II) report has offered foundational wisdom from 150 worldwide experts on ocular surface care and disease management, and provided guidance on best practices for management of conditions such as blepharitis.[1]

In addition, eye care professionals have access to treatments for blepharitis that address the inflammatory and sometimes bacterial aspects of the condition in order to relieve patient symptoms in a meaningful way.

The availability of effective and timely treatment can not only help to reduce the signs and symptoms of blepharitis for sufferers, but it can help to target unwanted physical manifestations of the condition that potentially weigh on the patient's psyche and negatively impact on their social experience.[2,3]

As DEWS II and other consensus documents continue to add to the collective body of eye care knowledge, clinicians can gain valuable insights on the most effective ways to care for their blepharitis patients. With this new information in mind, they can hope to promptly help alleviate the physical and social-emotional burdens of the condition for those who deal with it.

CHALLENGES OF BLEPHARITIS

Blepharitis is one of the most common ocular pathologies encountered in the clinical settings.[4] Reports from US primary eye care providers estimate that approximately 40% of patients seen present with signs or symptoms of blepharitis.[4] However, the etiology of blepharitis is poorly understood.[5] Pathogenesis is hypothesized to be multifactorial, to include inflammatory skin conditions, chronic lid margin infections, and parasitic infections.[6] Symptoms can include a foreign body or burning sensation, excessive tearing, itching, photophobia, red and swollen eyelids, redness of the eye, blurred vision, dry eye, and scurf on the eyelashes.[5]

Blepharitis is categorized as acute or chronic, and also by anatomic location: 1) anterior, which affects the exterior of the eyelid at the base of the eyelashes, and is frequently caused by bacteria (Staphylococcal) and seborrheic dermatitis;[5] and 2) posterior blepharitis, which is found at the posterior lid margin, and is frequently caused by meibomian gland dysfunction (MGD), infectious or allergic conjunctivitis, acne, rosacea and seborrheic dermatitis.[5] That said, in patients with infectious blepharitis, the associated pathogens and resulting inflammation don't tend to differentiate by location.

Despite its prevalence, blepharitis can be a challenging condition to treat.[7] If not adequately addressed, long-term, unmanaged blepharitis can lead to permanent changes to the eyelid morphology, and visual deficits due to keratopathy and corneal ulceration.[6]

Blepharitis, in addition to yielding unwanted

Please see Important Safety Information on page 6 and full Prescribing Information for ZYLET® (loteprednol etabonate 0.5% and tobramycin 0.3% ophthalmic suspension) on pages 7-8.

Caring for the Blepharitis Patient

Here is a short excerpt from our overall protocol for managing the average blepharitis patient.

Evaluation & Diagnosis

- Carefully evaluate the slit-lamp exam for MGD and dry eye disease; look for corneal staining
- Check for conjunctival involvement of follicles and papilla

Classification

- Determine acute vs. chronic nature of condition (anterior vs. posterior determination is less critical)

Lid Hygiene and Treatment Strategy

- Acute blepharitis: Short burst of combination topical antibiotic-corticosteroids
- Chronic blepharitis: Lid hygiene, hot compresses, and lid scrubs; oral antibiotics; and "episodic use" of combination topical antibiotic-corticosteroids

— Drs. Karpecki and Katsev

physical signs and symptoms for sufferers, can also take a negative emotional toll on patients. One study, a retrospective analysis, found that blepharitis patients were at elevated risk of anxiety and depression, particularly during the period shortly after diagnosis.[2] Another determined that persistently uncomfortable eyes, "an unattractive appearance," and uneasy feelings experienced by blepharitis patients might precipitate psychological stress and negative social implications.[3]

BLEPHAROKERATOCONJUNCTIVITIS

Blepharokeratoconjunctivitis (BKC), similar to blepharitis, is a chronic inflammatory condition of the palpebral margin; however, it also features secondary conjunctival and corneal involvement.[8] Signs and symptoms include tearing, photophobia, red eye, blepharitis (external hordeola or meibomian cysts), recurrent chalazia, phlyctenular conjunctivitis, keratitis, as well as corneal complications such as ulceration, neovascularization, scarring, and perforation.[8]

In our experience, BKC frequently leads to associated ocular surface inflammation, and it can exacerbate symptoms of coexisting ocular surface disease. One study found that patients with BKC had worse meibomian gland function, poorer morphology, and a higher rate of medical histories related to the meibomian gland than a healthy population.[9]

BLEPHARITIS MANAGEMENT & DEWS II

The chronic nature of blepharitis and the frequent coexistence of ocular surface disease can make blepharitis difficult to manage. Foundationally, patients who are prone to getting blepharitis should maintain good, routine eyelid hygiene in order to prevent flareups. One goal of management for blepharitis is to keep the lids clean and free of biofilm. Moreover, blepharitis patients who have concomitant acne rosacea should have the conditions treated simultaneously.

The importance of good lid hygiene was stressed by the authors of the DEWS II report.[1] The report's authors highlighted the importance of appropriately managing a variety of lid conditions that result in dry eye, particularly blepharitis.[1] Lid hygiene, if used correctly, the authors wrote, could reduce lipid byproducts and lipolytic bacteria associated with these conditions.[1] In addition, the International Workshop on Meibomian Gland Dysfunction put forth that lid hygiene has been widely considered an effective therapy for MGD and blepharitis.[10]

UPDATES IN LID HYGIENE PRACTICES

Applying warm compresses to the lids is often accepted as an essential first step for maintaining good lid hygiene. Traditionally, another hygiene strategy that had been employed for blepharitis patients for many years had been light scrubbing of the eyelids with a cotton swab coated with a mixture of water and baby shampoo. However, we have found that, over time, commercial shampoos can remove natural oils and key mucoproteins from our patients' meibomian glands.

Furthermore, the DEWS II report noted that outdated lid hygiene practices such as using diluted baby shampoo should be updated by eye care professionals. They specifically revealed that diluted baby shampoo has been associated with reduced ocular surface MUC5AC levels and might have an adverse effect on goblet cell function.[11]

As a result, the authors strongly advised that clinicians utilize newer, more efficacious hygiene

Please see Important Safety Information on page 6 and full Prescribing Information for ZYLET® (loteprednol etabonate 0.5% and tobramycin 0.3% ophthalmic suspension) on pages 7-8.

strategies available on the market today that utilize a diversity of delivery mechanisms to improve patient outcomes when it comes to lid hygiene.[1] They noted that many new products are available to improve lid health, including scrubs, foams, solutions, and wipes; however, more specific information was beyond the scope of the report.[1]

PATIENT ADHERENCE CHALLENGES

Research has found that patients who follow clinician-recommended lid hygiene practices can see symptom improvement. In a cross-sectional study, 207 subjects with dry eye symptoms and margin signs were instructed to perform warm compresses and eyelid scrubs, and then complete a follow-up phone survey assessing adherence and subjective therapeutic response six weeks later.[12] Patients who performed the routine noted an improvement in symptoms.[12]

However, one challenge for clinicians has been a lack of patient adherence with lid hygiene recommendations. The DEWS II authors noted that adherence to provider recommendations has been "notoriously poor."[1] In the aforementioned cross-sectional study, only 55% of patients were compliant after six weeks of use.[12] So, while eye care professionals may do their due diligence in instructing patients to maintain best practices with lid hygiene, it's uncertain whether patients will follow through with clinician instructions.

COMORBIDITY ISSUES

Even with adherence to regular lid hygiene practices, blepharitis may develop in predisposed patients. In these patients, the clinician must

Diagnosing BKC vs. Allergic Conjunctivitis or Dry Eye

It's important to reduce the risk of ocular complications in conditions such as BKC and rule out other ocular issues by confirming diagnosis as soon as possible. If dry eye is suspected, a positive result to a screening questionnaire such as the 5-item Dry Eye Questionnaire (DEQ-5) or the Ocular Surface Disease Index (OSDI) should trigger further evaluation.[15] Included are our recommended steps to follow to try to confirm BKC diagnosis:

Medical History Review

Triaging questions[16]

- Symptoms and signs
- Time of day when symptoms are worse
- Duration of symptoms
- Unilateral or bilateral presentation

Dry eye questionnaire[15]

- OSDI
- Standard patient evaluation of eye dryness (SPEED)

Risk factor analysis[16]

- Exacerbating conditions
- Systemic/autoimmune disease(s) that can contribute or cause BKC
- Recent exposure to an infected individual

Clinical examination[16]

- Eye chart or visual acuity test
- Skin and eyelids changes
- Slit lamp exam with fluorescein:
  - Tear break-up time (<10 sec)
  - Anterior and posterior eyelid margin
  - Eyelashes
  - Eyelids
  - Tarsal and bulbar conjunctiva
  - Cornea
  - Intraocular pressure (IOP)

Diagnostic tests[16]

There are no specific clinical diagnostic tests for blepharitis.

- Cultures of the eyelid margins for:
  - Recurrent anterior blepharitis with severe inflammtion
  - Patients who are not responding to therapy

However, normal lids will often culture positive for normal bacterial flora, so this strategy may not always be optimal.

15. Wolffsohn JS, Arita R, Chalmers R, et al. TFOS DEWS II Diagnostic Methodology Report. Ocul Surf. 2017 Jul;15(3):539-574.
16. Amescua G, Akpek EK, Farid M, et al. Blepharitis Preferred Practice Pattern®. Ophthalmology. 2019 Jan;126(1):P56-P93.

— Drs. Karpecki and Katsev

first take steps to make the correct diagnosis. Yet, diagnosing blepharitis can be less than straightforward at times.

For example, patient complaints of ocular itching may initially lead the eye care professional to suspect that ocular allergies are involved. Histamine, which is released as a result of ongoing exposure to an allergen, activates G protein-coupled histamine receptors on sensory neurons, signaling the brain to perceive an "itch" sensation,[13] commonly associated with ocular allergies. Yet, itching can also be induced in a histamine-independent manner by certain endogenous peptide fragments.[14] And blepharitis, *Demodex* mites, as well as a host of other conditions also share the symptom of itching, more specifically on the eyelids.

Diagnosing BKC can also be difficult due to the overlap of symptoms with allergic conjunctivitis and dry eye. However, key differences can help indicate which condition a patient is presenting with. For example, BKC symptoms tend to present in the eyelid either unilaterally or bilaterally, while symptoms in patients with allergic conjunctivitis are typically seen bilaterally and can also affect the ocular surface.[16,17] Dry eye, on the other hand, affects the ocular surface more than the eyelids.[18]

Certain guidelines can help the clinician distinguish between BKC and these other ocular conditions (*see "Diagnosing BKC vs. Allergic Conjunctivitis or Dry Eye" on page 3.)*

TREATMENT STRATEGIES

Beyond basic lid hygiene and after a diagnosis is made, choosing the right therapy to alleviate symptoms and signs for the blepharitis patient is key to positive outcomes. The treatment landscape today offers eye care professionals various tools to help manage or improve their blepharitis patients' signs and symptoms. As research continues to expand the collective body of knowledge on best practices for managing conditions such as blepharitis, eye care's understanding of how best to apply these potential therapies also evolves.

Importantly, the patient must understand that a cure for blepharitis is often not possible.[16] Treatments that may be helpful include: warm compresses; eyelid cleansing, including eyelid massage in cases of MGD to express the meibomian glands; antibiotics (topical and/or systemic); and topical anti-inflammatory agents (e.g., corticosteroids, cyclosporine).[16] These therapies are often used in combination.[16] Here is a more detailed list of some available treatments:

Over-The-Counter

• **Artificial Tears.** Tear film instability often accompanies blepharitis, so artificial tears may improve patient symptoms when used in conjunction with eyelid cleansing and medications.[16]

Prescription Drugs.

Treatments for some cases of blepharitis requiring a prescription include the following:

• **Anti-infectives** available as antibiotic eyedrops, creams, and ointments, or oral antibiotics when indicated.

• **Anti-inflammatory agents** such as steroid eyedrops, creams, or ointments.

• **Medications** that affect the immune system such as calcineurin inhibitors, which are designed to offer relief of some signs and symptoms of blepharitis.

• **Treatments for underlying conditions,** which are intended to control the issues leading to blepharitis.

• **Combination anti-infectives and anti-inflammatory agents** for patients in whom both therapies are indicated.

In-Office Procedures.

In addition, a number of in-office procedures can be conducted to help address blepharitis. They include the following:

• **Exfoliation of the lid margin,** designed to remove any mites and bacteria, and associated biofilm from the eyelids through debridement; as well as open any clogged meibomian glands

• **Thermal pulsation treatment,** designed to melt and evacuate meibum, and any material that is obstructing the meibomian glands.

• **Intense pulse light therapy,** designed to treat telangiectatic meibomian glands by bringing inflammatory mediators to the ocular surface.

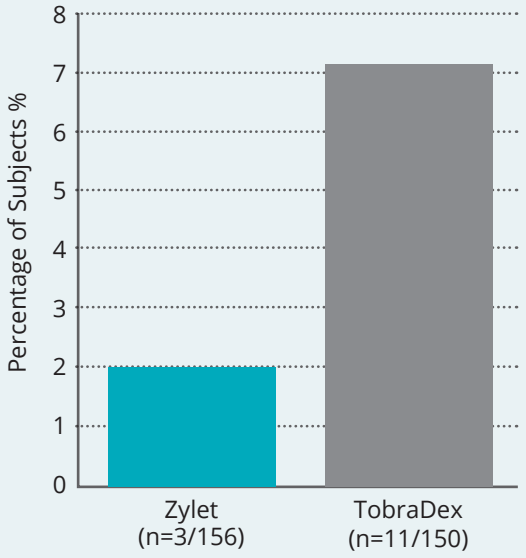
With in-office procedures, it is still important to make sure to address the microbial growth as well as the inflammatory aspects of blepharitis.

SELECTION OF THERAPIES FOR THE BLEPHARITIS PATIENTS

It is up to the clinician to select the appropriate therapy for their blepharitis patient in a medical landscape offering multiple options. One prescrip-

Please see Important Safety Information on page 6 and full Prescribing Information for ZYLET® (loteprednol etabonate 0.5% and tobramycin 0.3% ophthalmic suspension) on pages 7-8.

Subject in each study group with IOP changes >10 mmHg over baseline



In a randomized, double-masked, parallel-group study with healthy volunteers designed to evaluate the safety and tolerability of Zylet and TobraDex, treatment was administered four times a day in both eyes, for 28 days.[19] The primary endpoint was an increase in IOP ≥10 mmHg over baseline. IOP elevations at or above 10 mmHg were seen in 2% of Zylet-treated participants and 7.5% of TobraDex-treated participants.
If Zylet is used for 10 days or longer, IOP should be monitored.[20]

19. Holland EJ, Bartlett JD, Paterno MR, et al. Effects of loteprednol/tobramycin versus dexamethasone/tobramycin on intraocular pressure in healthy volunteers. Cornea. 2008;27:50-5.
20. ZYLET. Prescribing Information. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/050804s018lbl.pdf (last accessed Aug. 28, 2019).

tion therapy intended to help patients with blepharitis is a topical anti-infective and steroid combination for steroid responsive inflammatory ocular conditions for which a corticosteroid is indicated and where superficial bacterial ocular infection or a risk of bacterial ocular infection exists. The agent, Zylet® (loteprednol etabonate 0.5% and tobramycin 0.3% ophthalmic suspension), is formulated with the known moisturizing ingredients povidone and glycerin. Initially approved for use in the US in 2004,[20] Zylet and its attributes have been studied in clinical trials.

Data from one randomized, double-masked, parallel-group study with healthy volunteers evaluated the safety and tolerability of Zylet and TobraDex.[19] A total of 306 healthy volunteers received either loteprednol etabonate/tobramycin (n=156) or dexamethasone/tobramycin (n=150) at four-hour intervals, four times a day in both eyes for 28 days. Researchers found that Zylet was significantly less likely to produce elevations in IOP than TobraDex was in healthy subjects treated for 28 days.[19] Both drugs showed similar efficacy and were well-tolerated, with low risks for systemic and ocular adverse events other than elevation in IOP for dexamethasone/tobramycin.[19]

In a multicenter, randomized, investigator-masked, parallel-group study, investigators compared the safety and efficacy of Zylet and TobraDex in the treatment of ocular inflammation associated with BKC.[21] Subjects with clinically diagnosed blepharokeratoconjunctivitis in at least one eye were randomized to Zylet (n=138) or TobraDex (n=138) administered four times per day, for 14 days. The primary efficacy endpoint was the change from baseline to Day 15 (±1 day) in the signs and symptoms composite score using a non-inferiority metric to compare Zylet to TobraDex. Safety endpoints included visual acuity (VA), biomicroscopy, IOP assessments, and adverse events. At Day 15, the mean (SD) change from baseline in the signs and symptoms composite score was -15.2 (7.3) for Zylet-treated subjects and -15.6 (7.7) for TobraDex-treated subjects.[21] Subjects treated with TobraDex experienced a significant increase in IOP vs. those treated with Zylet at Day 7, Day 15, and overall.[21]

In some patients, we have found an "episodic treatment" strategy with Zylet to be particularly effective, although we caution patients about the possibility of IOP spikes with prolonged use of corticosteroids and without proper monitoring after 10 days. That withstanding, we choose to employ a drug such as Zylet, with established efficacy, two moisturizing ingredients that may be soothing, and with less of a proclivity to elevate IOP.

Dr. Karpecki is a practicing optometrist at the Kentucky Eye Institute in Lexington, Ky., and Dr. Katsev is a cornea, cararact and refractive surgeon at the Sansum Clinic in Santa Barbara, Calif.

INDICATIONS AND USAGE

ZYLET® (loteprednol etabonate 0.5% and tobramycin 0.3% ophthalmic suspension) is a topical anti infective and corticosteroid combination for steroid-responsive inflammatory ocular conditions for which a corticosteroid is indicated and where superficial bacterial ocular infection or a risk of bacterial ocular infection exists.

Ocular steroids are indicated in inflammatory conditions of the palpebral and bulbar conjunctiva, cornea and anterior segment of the globe such as allergic conjuncti-vitis, acne rosacea, superficial punctate keratitis, herpes zoster keratitis, iritis, cyclitis, and where the inherent risk of steroid use in certain infective conjunctivitides is accepted to obtain a diminution in edema and inflammation. They are also indicated in chronic anterior uveitis and corneal injury from chemical, radiation or thermal burns, or penetration of foreign bodies.

The use of a combination drug with an anti-infective component is indicated where the risk of superficial ocular infection is high or where there is an expectation that potentially dangerous numbers of bacteria will be present in the eye.

The particular anti-infective drug in this product (tobramycin) is active against the following common bacterial eye pathogens: Staphylococci, including *S. aureus* and *S. epidermidis* (coagulase-positive and coagulase-negative), including penicillin-resistant strains. Streptococci, including some of the Group A-beta-hemolytic species, some nonhemolytic species, and some *Streptococcus pneumoniae*, *Pseudomonas aeruginosa*, *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter aerogenes*, *Proteus mirabilis*, *Morganella morganii*, most *Proteus vulgaris* strains, *Haemophilus influenzae*, and *H. aegyptius*, *Moraxella lacunata*, *Acinetobacter calcoaceticus* and some *Neisseria* species.

IMPORTANT SAFETY INFORMATION

- ZYLET 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 infections of the eye and fungal diseases of ocular structures.
- Prolonged use of corticosteroids may result in glaucoma with damage to the optic nerve, and 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.
- Use of corticosteroids may result in posterior subcapsular cataract formation.
- 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 a slit lamp biomicroscopy and, where appropriate, fluorescein staining.
- Prolonged use of corticosteroids may suppress the host response and thus increase the hazard of secondary ocular infections. In acute purulent conditions, steroids may mask infection or enhance existing infections. If signs and symptoms fail to improve after 2 days, the patient should be re-evaluated.
- Employment of 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.
- Most common adverse reactions reported in patients were injection and superficial punctate keratitis, increased intraocular pressure, and burning and stinging upon instillation.

Please see full Prescribing Information for ZYLET (loteprednol etabonate 0.5% and tobramycin 0.3% ophthalmic suspension) on pages 7 & 8.

REFERENCES

1. Jones L, Downie LE, Korb D, et al. TFOS DEWS II Management and Therapy Report. Ocul Surf. 2017 Jul;15(3):575-628.
2. Chiang CC, Lin CL, Tsai YY, et al. Patients with blepharitis are at elevated risk of anxiety and depression. PLoS One. 2013 Dec 30;8(12):e83335.
3. McDonald MB. The patient's experience of blepharitis. Ocul Surf. 2009 Apr; 7(2 Suppl):S17-8.
4. Lemp MA, Nichols KK. Blepharitis in the United States 2009: a survey-based perspective on prevalence and treatment. Ocul Surf. 2009;7(Suppl 2):1–14.
5. Lindsley K, Matsumura S, Hatef E, et al. Interventions for chronic blepharitis. Cochrane Database Syst Rev. 2012 May 16;(5):CD005556.
6. Putnam CM. Diagnosis and management of blepharitis: an optometrist's per-spective. Clin Optom (Auckl). 2016 Aug 8;8:71-8.
7. Duncan K, Jeng BH. Medical management of blepharitis. Curr Opin Ophthal-mol. 2015 Jul;26(4):289-94.
8. Rodríguez-García A, González-Godínez S, López-Rubio S. Blepharokeratocon-junctivitis in childhood: corneal involvement and visual outcome. Eye (Lond). 2016 Mar;30(3):438-46.
9. Yin Y, Gong L. The evaluation of meibomian gland function, morphology and related medical history in Asian adult blepharokeratoconjunctivitis patients. Acta Ophthalmol. 2017 Sep;95(6):634-8. (last accessed Aug. 28, 2019).
10. Geerling G, Tauber J, Baudouin C, et al. The international workshop on meibomian gland dysfunction: report of the subcommittee on management and treatment of meibomian gland dysfunction. Invest Ophthalmol Vis Sci 2011;52(4):2050-64.
11. Sung J, Wang MTM, Lee SH, et al. Randomized double-masked trial of eyelid cleansing treatments for blepharitis. Ocul Surf. 2018;16(1):77-83.
12. Alghamdi YA, Camp A, Feuer W, et al. Compliance and subjective patient responses to eyelid hygiene. Eye Contact Lens. 2017;43(4):213-17.
13. Xiao B, Patapoutian A. Scratching the surface: a role of pain-sensing TRPA1 in itch. Nat Neurosci. 2011 May;14(5):540-2.
14. Sikand P, Dong X, Lamotte RH. BAM8-22 peptide produces itch and nocicep-tive sensations in humans independent of histamine release. J Neurosci. 2011 May 18;31(20):7563-7.
15. Wolffsohn JS, Arita R, Chalmers R, et al. TFOS DEWS II Diagnostic Methodology report. Ocul Surf. 2017 Jul;15(3):539-74.
16. Amescua G, Akpek EK, Farid M, et al. Blepharitis Preferred Practice Pat-tern®Ophthalmology. 2019 Jan;126(1):P56-93.
17. Ackerman S, Smith LM, Gomes PJ. Ocular itch associated with allergic conjunctivitis: latest evidence and clinical management. Ther Adv Chronic Dis. 2016;7:52-67.
18. Abelson MB, Lilyestrom L. Is it dry eye or allergy? Review of Optometry. 2007; Aug. 15. Available at: https://www.reviewofoptometry.com/article/is-it-dry-eye-or-allergy (last accessed Aug. 28, 2019).
19. Holland EJ, Bartlett JD, Paterno MR, et al. Effects of loteprednol/tobramycin versus dexamethasone/tobramycin on intraocular pressure in healthy volunteers. Cornea. 2008;27:50-5.
20. ZYLET. Prescribing Information. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/050804s018lbl.pdf (last accessed Aug. 28, 2019).
21. White EM, Macy JI, Bateman KM, et al. Comparison of the safety and effica-cy of loteprednol 0.5%/tobramycin 0.3% with dexamethasone 0.1%/tobramycin 0.3% in the treatment of blepharokeratoconjunctivitis. Curr Med Res Opin. 2008 Jan;24(1):287-96.

BAUSCH + LOMB

Zylet®

loteprednol etabonate 0.5%
and tobramycin 0.3%
ophthalmic suspension

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ZYLET® (loteprednol etabonate and tobramycin ophthalmic suspension) safely and effectively. See full prescribing information for ZYLET (loteprednol etabonate and tobramycin ophthalmic suspension, 0.5%/0.3%).

Zylet (loteprednol etabonate and tobramycin ophthalmic suspension) 0.5%/0.3%
Initial U.S. Approval: 2004

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

Zylet is a topical anti-infective and steroid combination for steroid-responsive inflammatory ocular conditions for which a corticosteroid is indicated and where superficial bacterial ocular infection or a risk of bacterial ocular infection exists. (1)

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

Apply one or two drops of Zylet into the conjunctival sac of the affected eye every four to six hours. (2.1)

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

Zylet contains 5 mg/mL loteprednol etabonate and 3 mg/mL tobramycin. (3)

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

Zylet, as with other steroid anti-infective ophthalmic combination drugs, 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. (4.1)

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

- Intraocular pressure (IOP)-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 a 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. If signs and symptoms fail to improve after 2 days, the patient should be re-evaluated. (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 ----------

Most common adverse reactions reported in patients were injection and superficial punctate keratitis, increased intraocular pressure, burning and stinging upon instillation. (6)

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.
See 17 for PATIENT COUNSELING INFORMATION.

Revised: 08/2016

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Zylet® is a topical anti-infective and corticosteroid combination for steroid-responsive inflammatory ocular conditions for which a corticosteroid is indicated and where superficial bacterial ocular infection or a risk of bacterial ocular infection exists.

Ocular steroids are indicated in inflammatory conditions of the palpebral and bulbar conjunctiva, cornea and anterior segment of the globe such as allergic conjunctivitis, acne rosacea, superficial punctate keratitis, herpes zoster keratitis, iritis, cyclitis, and where the inherent risk of steroid use in certain infective conjunctivitides is accepted to obtain a diminution in edema and inflammation. They are also indicated in chronic anterior uveitis and corneal injury from chemical, radiation or thermal burns, or penetration of foreign bodies.

The use of a combination drug with an anti-infective component is indicated where the risk of superficial ocular infection is high or where there is an expectation that potentially dangerous numbers of bacteria will be present in the eye.

The particular anti-infective drug in this product (tobramycin) is active against the following common bacterial eye pathogens:

Staphylococci, including *S. aureus* and *S. epidermidis* (coagulase-positive and coagulase-negative), including penicillin-resistant strains. Streptococci, including some of the Group A-beta-hemolytic species, some nonhemolytic species, and some *Streptococcus pneumoniae, Pseudomonas aeruginosa, Escherichia coli, Klebsiella pneumoniae, Enterobacter aerogenes, Proteus mirabilis, Morganella morganii*, most *Proteus vulgaris* strains, *Haemophilus influenzae*, and *H. aegyptius, Moraxella lacunata, Acinetobacter calcoaceticus* and some *Neisseria* species.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosing

Apply one or two drops of Zylet into the conjunctival sac of the affected eye every four to six hours. During the initial 24 to 48 hours, the dosing may be increased, to every one to two hours. Frequency should be decreased gradually as warranted by improvement in clinical signs. Care should be taken not to discontinue therapy prematurely.

2.2 Prescription Guideline

Not more than 20 mL should be prescribed initially and the prescription should not be refilled without further evaluation *[see Warnings and Precautions (5.3)]*.

3 DOSAGE FORMS AND STRENGTHS

Zylet (loteprednol etabonate and tobramycin ophthalmic suspension) 0.5%/0.3% contains 5 mg/mL loteprednol etabonate and 3 mg/mL tobramycin.

4 CONTRAINDICATIONS

4.1 Nonbacterial Etiology

Zylet, as with other steroid anti-infective ophthalmic combination drugs, 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.

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 a 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. If signs and symptoms fail to improve after 2 days, the patient should be re-evaluated.

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 Aminoglycoside Hypersensitivity

Sensitivity to topically applied aminoglycosides may occur in some patients. If hypersensitivity develops with this product, discontinue use and institute appropriate therapy.

6 ADVERSE REACTIONS

Adverse reactions have occurred with steroid/anti-infective combination drugs which can be attributed to the steroid component, the anti-infective component, or the combination.

Zylet:

In a 42-day safety study comparing Zylet to placebo, ocular adverse reactions included injection (approximately 20%) and superficial punctate keratitis (approximately 15%). Increased intraocular pressure was reported in 10% (Zylet) and 4% (placebo) of subjects. Nine percent (9%) of Zylet subjects reported burning and stinging upon instillation.

Ocular reactions reported with an incidence less than 4% include vision disorders, discharge, itching, lacrimation disorder, photophobia, corneal deposits, ocular discomfort, eyelid disorder, and other unspecified eye disorders.

The incidence of non-ocular reactions reported in approximately 14% of subjects was headache; all other non-ocular reactions had an incidence of less than 5%.

Loteprednol etabonate ophthalmic suspension 0.2% - 0.5%:

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.

In a summation of controlled, randomized studies of individuals treated for 28 days or longer with loteprednol etabonate, the incidence of significant elevation of intraocular pressure (≥10 mm Hg) was 2% (15/901) among patients receiving loteprednol etabonate, 7% (11/164) among patients receiving 1% prednisolone acetate and 0.5% (3/583) among patients receiving placebo.

Tobramycin ophthalmic solution 0.3%:

The most frequent adverse reactions to topical tobramycin are hypersensitivity and localized ocular toxicity, including lid itching and swelling and conjunctival erythema. These reactions occur in less than 4% of patients. Similar reactions may occur with the topical use of other aminoglycoside antibiotics.

Secondary Infection:

The development of secondary infection has occurred after use of combinations containing steroids and antimicrobials. Fungal infections of the cornea are particularly prone to develop coincidentally with long-term applications of steroids.

The possibility of fungal invasion must be considered in any persistent corneal ulceration where steroid treatment has been used.

Secondary bacterial ocular infection following suppression of host responses also occurs.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic effects: Loteprednol etabonate has been shown to be embryotoxic (delayed ossification) and teratogenic (increased incidence of meningocele, abnormal left common carotid artery, and limb fixtures) 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 at 0.5 mg/kg/day (6 times the maximum daily 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.

Reproductive studies have been performed in rats and rabbits with tobramycin at doses up to 100 mg/kg/day parenterally and have revealed no evidence of impaired fertility or harm to the fetus. There are no adequate and well-controlled studies in pregnant women. Zylet 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 that appear in human milk could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. Caution should be exercised when Zylet is administered to a nursing woman.

8.4 Pediatric Use

Two trials were conducted to evaluate the safety and efficacy of Zylet® (loteprednol etabonate and tobramycin ophthalmic suspension) in pediatric subjects age zero to six years; one was in subjects with lid inflammation and the other was in subjects with blepharoconjunctivitis.

In the lid inflammation trial, Zylet with warm compresses did not demonstrate efficacy compared to vehicle with warm compresses. Patients received warm compress lid treatment plus Zylet or vehicle for 14 days. The majority of patients in both treatment groups showed reduced lid inflammation.

In the blepharoconjunctivitis trial, Zylet did not demonstrate efficacy compared to vehicle, loteprednol etabonate ophthalmic suspension, or tobramycin ophthalmic solution. There was no difference between treatment groups in mean change from baseline blepharoconjunctivitis score at Day 15.

There were no differences in safety assessments between the treatment groups in either trial.

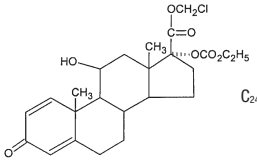
8.5 Geriatric Use

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

11 DESCRIPTION

Zylet (loteprednol etabonate and tobramycin ophthalmic suspension) is a sterile, multiple dose topical anti-inflammatory corticosteroid and anti-infective combination for ophthalmic use. Both loteprednol etabonate and tobramycin are white to off-white powders. The chemical structures of loteprednol etabonate and tobramycin are shown below.

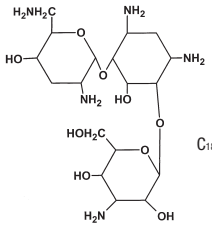
Loteprednol etabonate:



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

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

Tobramycin:



$C_{18}H_{37}N_5O_9$ Mol. Wt. 467.52

Chemical Name:

O-3-Amino-3-deoxy-α-D-glucopyranosyl-(1→4)-O-[2,6-diamino-2,3,6-trideoxy-α-D-ribo-hexopyranosyl-(1→6)]-2-deoxystreptamine

Each mL contains: Actives: Loteprednol Etabonate 5 mg (0.5%) and Tobramycin 3 mg (0.3%). Inactives: Edetate Disodium, Glycerin, Povidone, Purified Water, Tyloxapol, and Benzalkonium Chloride 0.01% (preservative). Sulfuric Acid and/or Sodium Hydroxide may be added to adjust the pH to 5.7-5.9. The suspension is essentially isotonic with a tonicity of 260 to 320 mOsm/kg.

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. There is no generally accepted explanation for the mechanism of action of ocular corticosteroids. However, corticosteroids are thought to act by the induction of phospholipase A_2 inhibitory proteins, collectively called lipocortins. It is postulated that these proteins control the biosynthesis of potent mediators of inflammation such as prostaglandins and leukotrienes by inhibiting the release of their common precursor arachidonic acid.

Arachidonic acid is released from membrane phospholipids by phospholipase A_2. Corticosteroids are capable of producing a rise in intraocular pressure.

Loteprednol etabonate is structurally similar to other corticosteroids. However, the number 20 position ketone group is absent.

The anti-infective component in the combination (tobramycin) is included to provide action against susceptible organisms. *In vitro* studies have demonstrated that tobramycin is active against susceptible strains of the following microorganisms:

Staphylococci, including *S. aureus* and *S. epidermidis* (coagulase-positive and coagulase-negative), including penicillin-resistant strains.

Streptococci, including some of the Group A-beta-hemolytic species, some nonhemolytic species, and some *Streptococcus pneumoniae. Pseudomonas aeruginosa, Escherichia coli, Klebsiella pneumoniae, Enterobacter aerogenes, Proteus mirabilis, Morganella morganii,* most *Proteus vulgaris* strains, *Haemophilus influenzae* and *H. aegyptius, Moraxella lacunata, Acinetobacter calcoaceticus* and some *Neisseria* species.

12.3 Pharmacokinetics

In a controlled clinical study of ocular penetration, the levels of loteprednol etabonate in the aqueous humor were found to be comparable between Lotemax and Zylet treatment groups.

Results from a bioavailability study in normal volunteers established that plasma levels of loteprednol etabonate and Δ1 cortienic acid etabonate (PJ 91), its primary, inactive metabolite, were below the limit of quantitation (1 ng/mL) at all sampling times.

The results were obtained following the ocular administration of one drop in each eye of 0.5% loteprednol etabonate ophthalmic suspension 8 times daily for 2 days or 4 times daily for 42 days. This study suggests that limited (<1 ng/mL) systemic absorption occurs with 0.5% loteprednol etabonate.

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 or tobramycin.

Loteprednol etabonate was not genotoxic *in vitro* in the Ames test, the mouse lymphoma TK assay, a chromosome aberration test in human lymphocytes, or in an *in vivo* mouse micronucleus assay.

Oral treatment of male and female rats at 50 mg/kg/day and 25 mg/kg/day of loteprednol etabonate, respectively, (500 and 250 times the maximum clinical dose, respectively) prior to and during mating did not impair fertility in either gender. No impairment of fertility was noted in studies of subcutaneous tobramycin in rats at 100 mg/kg/day (1700 times the maximum daily clinical dose).

16 HOW SUPPLIED/STORAGE AND HANDLING

Zylet (loteprednol etabonate and tobramycin ophthalmic suspension) is supplied in a white low density polyethylene plastic bottle with a white controlled drop tip and a white polypropylene cap in the following sizes:

5 mL (NDC 24208-358-05) in a 7.5 mL bottle

10 mL (NDC 24208-358-10) in a 10 mL bottle

USE ONLY IF IMPRINTED NECKBAND IS INTACT.

Storage: Store upright at 15º-25ºC (59º-77ºF). PROTECT FROM FREEZING. SHAKE VIGOROUSLY BEFORE USING.

17 PATIENT COUNSELING INFORMATION

This product is sterile when packaged. Patients should be advised not to allow the dropper tip to touch any surface, as this may contaminate the suspension. If pain develops, redness, itching or inflammation becomes aggravated, the patient should be advised to consult a physician. As with all ophthalmic preparations containing benzalkonium chloride, patients should be advised not to wear soft contact lenses when using Zylet.

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

9007706 (FOLDED)
9004406 (FLAT)