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Making Strides in Blepharitis Treatment

How New Insights Can Help Clinicians Elevate Patient Care

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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

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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

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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

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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.

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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-

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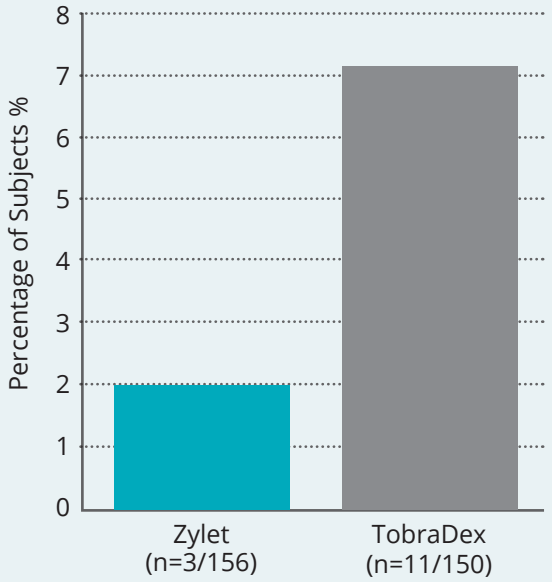
Subject in each study group with IOP changes >10 mmHg over baseline



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 [package insert]. Tampa, FL: Bausch & Lomb Incorporated; 2021.

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.

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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 conjunctivitis, acne rosacea, superficial punctate keratitis, herpes zoster keratitis, iritis, cyclitis, and where the inherent risk of steroid use in certain infective conjunctivitis 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 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. 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.
- Sensitivity to topically applied aminoglycosides may occur in some patients. If hypersensitivity develops, discontinue use and institute appropriate therapy.
- Do not allow the dropper tip to touch any surface, as this may contaminate the suspension.
- Advise patients not to wear soft contact lenses when using ZYLET.
- Most common adverse reactions reported in patients were injection and superficial punctate keratitis, increased intraocular pressure, burning and stinging upon instillation. The most common non-ocular reaction was headache.

You are encouraged to report side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch or call 1-800-FDA-1088.

Please see full Prescribing Information for ZYLET (loteprednol etabonate 0.5% and tobramycin 0.3% ophthalmic suspension) on pages 7–9.

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Please see Important Safety Information on page 6 and full Prescribing Information for ZYLET® on pages 7-9.

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ZYLET safely and effectively. See full prescribing information for ZYLET.

ZYLET® (loteprednol etabonate and tobramycin ophthalmic suspension) 0.5%/0.3%, for topical ophthalmic use

Initial U.S. Approval: 2004

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

ZYLET is a combination of loteprednol etabonate, a corticosteroid, and tobramycin, an aminoglycoside antibacterial, indicated 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 ----------

Ophthalmic suspension containing 5 mg/mL (0.5%) loteprednol etabonate and 3 mg/mL (0.3%) 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) 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 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 Incorporated at 1-800-321-4576 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 10/2021

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

ZYLET® (loteprednol etabonate and tobramycin ophthalmic suspension), 0.5%/0.3% 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

Ophthalmic suspension containing 5 mg/mL (0.5%) loteprednol etabonate and 3 mg/mL (0.3%) 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.

5.8 Risk of Contamination

Do not allow the dropper tip to touch any surface, as this may contaminate the suspension.

5.9 Contact Lens Wear

As with all ophthalmic preparations containing benzalkonium chloride, patients should be advised not to wear soft contact lenses when using ZYLET.

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

Risk Summary

There are no adequate and well-controlled studies with loteprednol etabonate or tobramycin in pregnant women.

Loteprednol etabonate produced teratogenicity at clinically relevant doses in the rabbit and rat when administered orally during pregnancy. Loteprednol etabonate produced malformations when administered orally to pregnant rabbits at doses ≥ 0.54 times the recommended human ophthalmic dose (RHOD) and to pregnant rats at doses ≥ 13 times the RHOD. In pregnant rats receiving oral doses of loteprednol etabonate during the period equivalent to the last trimester of pregnancy through lactation in humans, survival of offspring was reduced at doses ≥ 1.3 times the RHOD. Maternal toxicity was observed in rats at doses ≥ 135 times the RHOD, and a maternal no observed adverse effect level (NOAEL) was established at 13 times the RHOD.

Abortions were observed in pregnant rabbits administered tobramycin via subcutaneous injection at 180 times the RHOD. Tobramycin did not affect fetal development when administered by subcutaneous injection to pregnant rats at doses 450 times the RHOD.

The background risk of major birth defects and miscarriage for the indicated population is unknown. However, the background risk in the U.S. general population of major birth defects is 2 to 4%, and of miscarriage is 15 to 20%, of clinically recognized pregnancies.

Data

Animal Data

Embryofetal studies were conducted in pregnant rabbits administered loteprednol etabonate by oral gavage on gestation days 6 to 18, to target the period of organogenesis. Loteprednol etabonate produced fetal malformations at doses ≥ 0.1 mg/kg/day (0.54 times the recommended human ophthalmic dose (RHOD) based on body surface area, assuming 100% absorption of loteprednol etabonate). Spina bifida (including meningocele) was observed at doses ≥ 0.1 mg/kg/day, and exencephaly and craniofacial malformations were observed at doses ≥ 0.4 mg/kg/day (2.1 times the RHOD). At 3 mg/kg/day (16 times the RHOD), loteprednol etabonate was associated with increased incidences of abnormal left common carotid artery, limb flexures, umbilical hernia, scoliosis, and delayed ossification. Abortion and embryofetal lethality (resorption) occurred at doses ≥ 6 mg/kg/day (32 times the RHOD). A NOAEL for developmental toxicity was not established in this study. The NOAEL for maternal toxicity in rabbits was 3 mg/kg/day.

Embryofetal studies were conducted in pregnant rats administered loteprednol etabonate by oral gavage on gestation days 6 to 15, to target the period of organogenesis. Loteprednol etabonate produced fetal malformations, including absent innominate artery at doses ≥ 5 mg/kg/day (13 times the RHOD); and cleft palate, agnathia, cardiovascular defects, umbilical hernia, decreased fetal body weight and decreased skeletal ossification at doses ≥ 50 mg/kg/day (135 times the RHOD). Embryofetal lethality (resorption) was observed at 100 mg/kg/day (270 times the RHOD). The NOAEL for developmental toxicity in rats was 0.5 mg/kg/day (1.3 times the RHOD). Loteprednol etabonate was maternally toxic (reduced body weight gain) at doses of ≥ 50 mg/kg/day. The NOAEL for maternal toxicity was 5 mg/kg/day.

A peri-/postnatal study was conducted in rats administered loteprednol etabonate by oral gavage from gestation day 15 (start of fetal period) to postnatal day 21 (the end of lactation period). At doses ≥ 0.5 mg/kg/day (1.3 times the RHOD), reduced survival was observed in live-born offspring. Doses ≥ 5 mg/kg/day (13 times the RHOD) caused umbilical hernia/incomplete gastrointestinal tract. Doses ≥ 50 mg/kg/day (135 times the RHOD) produced maternal toxicity (reduced body weight gain, death), decreased number of live-born offspring, decreased birth weight, and delays in postnatal development. A developmental NOAEL was not established in this study. The NOAEL for maternal toxicity was 5 mg/kg/day.

An embryofetal study was conducted in pregnant rabbits administered 20 or 40 mg/kg/day tobramycin by subcutaneous injection on gestational days 6 to 18, to target the period of organogenesis. Abortions and maternal toxicity (renal nephrosis and cortical tubular necrosis) were observed at both dose levels. The developmental and maternal lowest observed adverse effect level (LOAEL) is 20 mg/kg/day (180 times the RHOD based on body surface area, assuming 100% absorption of tobramycin). An embryofetal study was conducted in pregnant rats administered 50 or 100 mg/kg/day tobramycin by subcutaneous injection on gestational days 6 to 15, to target the period of organogenesis. No effects on development, reproduction, or maternal toxicity were reported. The developmental and maternal NOAEL is 100 mg/kg/day (450 times the RHOD).

8.2 Lactation

There are no data on the presence of loteprednol etabonate or tobramycin in human milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered, along with the mother's clinical need for ZYLET and any potential adverse effects on the breastfed infant from ZYLET.

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.

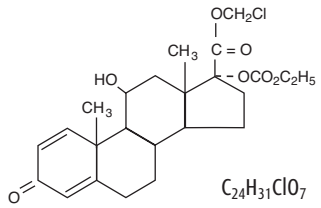
8.5 Geriatric Use

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.

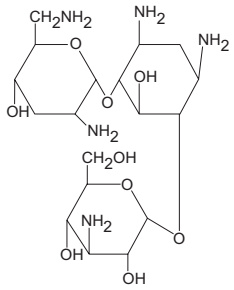
Loteprednol etabonate:



$C_{24}H_{31}ClO_7$ 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 5.5 to 6.2. 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 Δ^1 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

Carcinogenesis

Long-term animal studies have not been conducted to evaluate the carcinogenic potential of loteprednol etabonate or tobramycin.

Mutagenesis

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.

Impairment of Fertility

Oral treatment of female and male rats with 25 mg/kg/day of loteprednol etabonate (67 times the RHOD based on body surface area, assuming 100% absorption) prior to and during mating caused preimplantation loss and decreased the number of live fetuses/live births. The NOAEL for fertility in rats was 5 mg/kg/day (13 times the RHOD). Subcutaneous administration of male and female rats with tobramycin did not affect mating behavior or cause impairment of fertility at 100 mg/kg/day (450 times the RHOD based on body surface area, assuming 100% absorption).

16 HOW SUPPLIED/STORAGE AND HANDLING

ZYLET (loteprednol etabonate and tobramycin ophthalmic suspension) 0.5%/0.3% 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:

NDC 24208-358-05 5 mL fill in a 7.5 mL bottle

NDC 24208-358-10 10 mL fill in a 10 mL bottle

USE ONLY IF IMPRINTED NECKBAND IS INTACT.

Storage: Store upright at 15ºC to 25ºC (59ºF to 77ºF). PROTECT FROM FREEZING. SHAKE VIGOROUSLY BEFORE USING. After opening, ZYLET can be used until the expiration date on the bottle.

17 PATIENT COUNSELING INFORMATION

Risk of Contamination

This product is sterile when packaged. Advise patients not to allow the dropper tip to touch any surface, as this may contaminate the suspension.

Risk of Secondary Infection

Advise patients to consult a physician if pain develops, redness, itching or inflammation becomes aggravated.

Contact Lens Wear

As with all ophthalmic preparations containing benzalkonium chloride, advise patients not to wear soft contact lenses when using ZYLET.

Distributed by:
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