

BLEPHARITIS MANAGEMENT

A CLINICAL APPROACH

John R. Favetta, MD

Blepharitis refers to a variety of eyelid conditions with multiple, often concomitant, etiologies. Characterized by eyelid inflammation, bacterial overgrowth or infection—or the risk of infection—is also frequently present in blepharitis. As definitions and sub-categories of blepharitis have changed over the years, clear-cut estimates of prevalence have been challenging to obtain; but blepharitis is very frequently seen in ophthalmology practices. Left untreated, the presence of blepharitis may affect the risk of infection following ocular surgery and can limit the success of contact lens wear. A detailed history and careful attention to the lids, lashes, and meibomian glands during the slit lamp examination will aid in blepharitis detection and diagnosis. At a minimum, treatment includes eyelid hygiene; and acute presentations may benefit from combined antiinflammatory/antiinfective therapy. Combination agents can be particularly useful in the treatment of blepharitis.

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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 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.

Blepharitis is a catchall term encompassing the many, often overlapping, inflammatory and infectious conditions of the eyelids. Without a single, etiology-based definition, it has not been possible to gain a good idea of the prevalence of blepharitis. But the conditions that comprise blepharitis are among the most common encountered in a comprehensive ophthalmology practice.¹ Indeed, nearly a third of the patients I see—from young adults to seniors—present with signs and/or symptoms of blepharitis.

It is often useful to distinguish types of blepharitis based on anatomical location. Thus, we have anterior blepharitis, which affects the area around the lashes and follicles, and posterior blepharitis, which affects the meibomian glands and proximate tissues. In either form, multiple causative factors and disease processes may be involved; and anterior and posterior blepharitis often coexist.

Comorbidities, including chalazion and hordeolum, conjunctivitis, keratopathy (from superficial punctate keratitis to peripheral ulceration), and dry eye disease may be present with blepharitis.²

Blepharitis affects a broad swath of our patients: we see it in younger patients, who may have associated seborrheic dermatitis or acne rosacea; we see it in contact lens wearers, and in candidates for refractive, cataract, or other ocular surgeries; and we see it in patients who come in simply because they are bothered by its symptoms. I consider it imperative to treat even mild blepharitis, as treatment can reduce the risk of infection and inflammation, and—of particular importance to me as a surgeon—help ensure success for surgical candidates.

PATHOGENESIS

Anterior blepharitis is often associated with excessive bacterial growth on the lid margins. The microbes involved are typically the same species that normally reside there, including *Staphylococcus epidermidis* and *Staphylococcus aureus*.² While questions remain about the role(s) of bacteria in blepharitis, it appears that toxic exoenzymes produced by the colonizing species—particularly *S. epidermidis*—irritate the eyelids and ocular surface, causing the release of inflammatory mediators.¹

In some cases, altered meibomian gland secretions may be an initiating factor, offering a supportive environment for bacterial proliferation.³ But bacteria can also alter ocular surface lipids. For example, lipolytic staphylococcal enzymes break down the wax and sterol esters in the tear film; and the release of irritating breakdown products, including free fatty acids, as well as the resulting tear film instability, contribute to inflammation of the lid margin and conjunctiva.²

A number of potential non-microbial factors (eg, age and hormonal changes, medication use) can contribute to the changes in meibum quality and the ductal keratinization that underlies posterior blepharitis.³ Obstructive meibomian gland dysfunction (MGD) may not be inflammatory in its early stages, but the tear

film changes (instability and hyperosmolarity), ocular surface irritation, increased ductal pressure, and bacterial involvement all contribute to inflammation and frank posterior blepharitis.³

DIAGNOSIS

In blepharitis diagnosis, history is paramount. Questioning patients about their ocular symptoms throughout the day can be very revealing: when patients describe stickiness and burning upon waking, with improvement through the day and a worsening in the evening, I know to look closely for signs of posterior blepharitis on my examination.

Patients with anterior blepharitis report a gamut of symptoms. Some patients have red and swollen lids; others complain of irritation and burning. Contact lens wearers with anterior or posterior blepharitis may report discomfort and significantly reduced wearing time.

A close look at the lids forms a key part of the examination. Patients with anterior blepharitis often have reddened, swollen lids, telangiectasia, and debris or collarettes along the lashes. In addition, the tear meniscus may be foamy, a result of bacterial lipases causing breakdown of the meibomian lipids. In posterior blepharitis, we often see plugged, pouting meibomian glands that yield turbid, viscous meibum—or no meibum at all. Diagnostic gland expression is helpful in evaluating and grading a patient's underlying MGD.

Again, because either anterior or posterior blepharitis can affect the ocular surface, corneal and conjunctival staining with lissamine green, rose bengal, or fluorescein can help identify tissue changes indicative of blepharoconjunctivitis or blepharokeratoconjunctivitis.

TREATMENT

Eyelid hygiene is a mainstay of my treatment regimen for virtually every stage and subtype of blepharitis. Cleaning the crust, keratinized tissue, and bacteria and bacterial byproducts off the lid margin removes some contributors to the condition. I recommend any of several commercially available lid cleansing pads for my patients, giving a brief demonstration of their use in the office.

For patients with posterior blepharitis, especially, I also add a hot compress and massage step to follow the cleansing scrub; an omega-3 fatty acid dietary supplement may also be part of the regimen.^{4,5} Lid hygiene may be performed once or twice a day; in cases where I add a topical pharmaceutical agent, I tell patients to instill their final dose of drug after performing their bedtime lid cleaning and warm compresses.

Because blepharitis is often chronic and recurring, I emphasize to patients that even after we bring their acute condition under control, continued eyelid hygiene and warm compresses will help them maintain a healthy ocular surface.

Please see the Indications and Usage and Important Safety Information on page 2, and Prescribing Information for ZYLET on pages 5, 6 and 7.

CASE STUDY: PREOPERATIVE BLEPHARITIS

A 65-year-old male patient presented to our clinic complaining of decreased vision, which upon examination was attributable to cataract. The patient was motivated to undergo surgery, but because the examination also revealed significant lid swelling, telangiectasia, and inspissated meibomian glands, I opted to delay the operation in order to address his blepharitis.

I explained to the patient that treating his inflamed and possibly infected eyelids was important prior to undergoing ocular surgery. I believe that we have the best chance for a good surgical result when the lids and ocular surface are healthy at the outset.

In addition to a routine of eyelid hygiene and warm compresses, I prescribed ZYLET four times a day for 2 weeks. When the patient returned, his IOP was normal and the redness and edema of his lid margins had greatly decreased. In my opinion, the patient responded to ZYLET therapy.

At this point, I felt comfortable scheduling the patient for surgery—but I did make clear to him that blepharitis is a chronic condition; and that while his blepharitis was under control at the moment, he would need to continue regular eyelid hygiene and warm compresses, and to return to our office in the event of a significant flare-up.

PHARMACOLOGIC INTERVENTION

Lid hygiene alone is often insufficient to bring the coexisting and mutually reinforcing inflammatory and infectious aspects of blepharitis under control. Topical corticosteroids, powerful inhibitors of inflammation, can be extremely useful for treating the acutely inflamed lid margin and ocular surface. The risks associated with corticosteroid use—particularly increased intraocular pressure (IOP) and cataractogenesis—are important considerations when selecting an agent and determining the duration of therapy.

In many cases, the presence of bacterial overgrowth and the risk of superficial ocular infection also warrant the use of an antibiotic in treating blepharitis.⁶ A combination antibiotic/steroid agent is therefore well suited to address both the inflammatory and the potentially infectious components of this condition.

My agent of choice for treating blepharitis is ZYLET (loteprednol etabonate and tobramycin ophthalmic suspension 0.5%/0.3%). The steroid component, loteprednol etabonate 0.5%, is one key reason I favor ZYLET in the treatment of blepharitis.

Loteprednol etabonate combines antiinflammatory potency with an established safety profile.^{6,7} The loteprednol etabonate molecule contains an ester group in place of a ketone at the C-20 position. In the eye, the drug undergoes predictable hydrolysis into inactive metabolites, which is thought to contribute to its safety profile.^{6,7}

Tobramycin, the antibiotic in ZYLET, is broadly effective against common ocular pathogens, including the staphylococci often implicated in blepharitis.^{6,8}

I typically prescribe ZYLET QID for 10 to 14 days, depending on severity. To this I add eyelid hygiene and, where applicable, warm compresses and omega-3 supplements. I bring patients back within about 10 days to evaluate sign and symptom resolution and to check IOP. When I prescribe ZYLET for blepharitis, I emphasize to patients that it is intended as short-term therapy only, and that long-term continuation of eyelid hygiene should help reduce the likelihood of recurrence.

CONCLUSION

Paying close attention to the lid margins can be beneficial for patients and practitioners. Neither a pristine surgical outcome nor successful contact lens wear is likely without a healthy ocular surface. Indeed, I have postponed surgeries for patients who present with significant blepharitis. To help get the acute inflammation and bacterial overgrowth of blepharitis under control, treatment with ZYLET can be important.

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REFERENCES

1. Lemp MA, Nichols KK. Blepharitis in the United States 2009: A survey-based perspective on prevalence and treatment. *Ocul Surf.* 2009;7(2 Suppl):S1-S14.
2. Jackson WB. Blepharitis: current strategies for diagnosis and management. *Can J Ophthalmol.* 2008;43:170-9.
3. Nichols KK, Foulks GN, Bron AJ, et al. The international workshop on meibomian gland dysfunction: executive summary. *Invest Ophthalmol Vis Sci.* 2011;52(4):1922-9.
4. Macsai MS. The role of omega-3 dietary supplementation in blepharitis and meibomian gland dysfunction (an AOS thesis). *Trans Am Ophthalmol Soc.* 2008;106:336-56.
5. Olenik A, Jimenez-Alfaro I, Alejandre-Alba N, Mahillo-Fernandez I. A randomized, double-masked study to evaluate the effect of omega-3 fatty acids supplementation in meibomian gland dysfunction. *Clin Interv Aging.* 2013;8:1133-8.
6. Comstock TL, Holland EJ. Loteprednol and tobramycin in combination: a review of their impact on current treatment regimens. *Expert Opin Pharmacother.* 2010;11(5):843-50.
7. Chen M, Gong L, Sun X, et al. A multicenter, randomized, parallel-group, clinical trial comparing the safety and efficacy of loteprednol etabonate 0.5%/tobramycin 0.3% with dexamethasone 0.1%/tobramycin 0.3% in the treatment of Chinese patients with blepharokeratoconjunctivitis. *Curr Med Res Opin.* 2012;28(3):385-94.
8. ZYLET [package insert]. Tampa, FL: Bausch & Lomb Incorporated; 2016.

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Please see the Indications and Usage and Important Safety Information on page 2, and Prescribing Information for ZYLET on pages 5, 6 and 7.

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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

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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 conjunctivides 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.

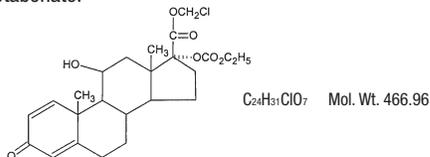
8.5 Geriatric Use

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

11 DESCRIPTION

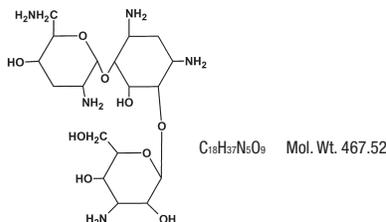
Zylet (loteprednol etabonate and tobramycin ophthalmic suspension) is a sterile, multiple dose topical anti-inflammatory corticosteroid and anti-infective combination for ophthalmic use. Both loteprednol etabonate and tobramycin are white to off-white powders. The chemical structures of loteprednol etabonate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

Loteprednol etabonate:



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

Tobramycin:



Chemical Name:

0-3-Amino-3-deoxy- α -D-glucopyranosyl-(1 \rightarrow 4)-O-[2,6-diamino-2,3,6-trideoxy- α -D-ribo-hexopyranosyl-(1 \rightarrow 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 A₂ 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 A₂. 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 cortic 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 15°-25°C (59°-77°F). 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
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