CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

50-804 (formerly 21-675)

Medical Review(s)

CLINICAL REVIEW #3 of NDA 50-804

M.O. Review #3
Clinical Amendments to Original NDA

Submitted:	December 7, 2004; December 8, 2004; December 9, 2004; December 10, 2004; December 13, 2004
Review completed:	December 13, 2004
Reviewer:	Lucious Lim, M.D., M.P.H.
Proposed Tradename:	Zylet
Established Name:	Loteprednol etabonate 0.5%/tobramycin 0.3% ophthalmic suspension
Sponsor:	Bausch & Lomb 8500 Hidden River Parkway Tampa, FL 33637 (813) 866-2299 Contact: Julie Townsend
Pharmacologic Category:	Corticosteroid/anti-infective combination
Proposed Indication:	Treatment of non-infectious posterior uveitis
Dosage Form and Route of Administration:	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

Submitted:

Submitted are Sponsor's final proposed package insert, container labels, and carton labels, and written commitment to perform a study in pediatric patients. The Sponsor commits to perform a pediatric study in a minimum of 60 patients 0 to 6 years of age to be completed within 24 months of the NDA's approval.

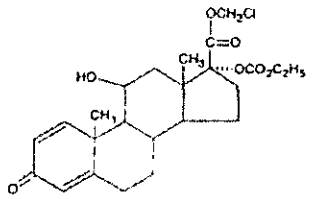
The final proposed package insert, container labels, and carton labels are acceptable. Following is the final package insert.

Zylet™
loteprednol etabonate 0.5% and tobramycin 0.3% ophthalmic suspension

STERILE

DESCRIPTION:
Zylet (loteprednol etabonate and tobramycin ophthalmic suspension), is a sterile, multiple dose topical anti-inflammatory corticosteroid and antibiotic 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.

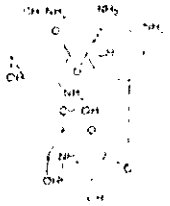
Loteprednol etabonate:



$C_{24}H_{31}ClO_7$ 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 mOsmol/kg.

CLINICAL PHARMACOLOGY:
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. It is highly lipid soluble which enhances its penetration into cells. Loteprednol etabonate is synthesized through structural modifications of prednisolone-related compounds so that it will undergo a predictable transformation to an inactive metabolite. Based upon *in vivo* and *in vitro* preclinical metabolism studies, loteprednol etabonate undergoes extensive metabolism to inactive carboxylic acid metabolites.

The antibiotic 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.

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.

INDICATIONS AND USAGE:
Zylet is 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.

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.

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. Zylet is also contraindicated in individuals with known or suspected hypersensitivity to any of the ingredients of this preparation and to other corticosteroids.

WARNINGS:
NOT FOR INJECTION INTO THE EYE.
Prolonged use of corticosteroids may result in glaucoma with damage to the optic nerve, defects in visual acuity and fields of vision, and in posterior subcapsular cataract formation. Steroids should be used with caution in the presence of glaucoma. Sensitivity to topically applied aminoglycosides may occur in some patients. If sensitivity reaction does occur, discontinue use.

Prolonged use of corticosteroids may suppress the host response and thus increase the hazard of secondary ocular infections. In those diseases causing thinning of the cornea or sclera, perforations have been known to occur with the use of topical steroids. In acute purulent conditions of the eye, steroids may mask infection or enhance existing infection.

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

The use of steroids after cataract surgery may delay healing and increase the incidence of bleb formation.

PRECAUTIONS:

General: For ophthalmic use only. The initial prescription and renewal of the medication order beyond 14 days should be made by a physician only after examination of the patient with the aid of magnification, such as slit lamp biomicroscopy and, where appropriate, fluorescein staining.

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

If this product is used for 10 days or longer, intraocular pressure should be monitored even though it may be difficult in children and uncooperative patients (See WARNINGS).

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.

As with other antibiotic preparations, prolonged use may result in overgrowth of nonsusceptible organisms, including fungi. If superinfection occurs, appropriate therapy should be initiated.

Cross-sensitivity to other aminoglycoside antibiotics may occur; if hypersensitivity develops with this product, discontinue use and institute appropriate therapy.

Information for Patients:

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.

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).

Pregnancy:

Teratogenic effects: Pregnancy Category C.

Loteprednol etabonate was shown to be teratogenic when administered orally to rats and rabbits during organogenesis at 5 and 3 mg/kg/day, respectively (50 and 30 times the maximum daily clinical dose in rats and rabbits, respectively). An oral dose of loteprednol etabonate in rats at 50

mg/kg/day (500 times the maximum daily clinical dose) during late pregnancy through the weaning period showed a decrease in the growth and survival of pups without dystocia. However, no adverse effect in the pups was observed at 5 mg/kg/day (50 times the maximum daily clinical dose).

Parenteral doses of tobramycin did not show any harm to fetuses up to 100 mg/kg/day (1700 times the maximum daily clinical dose) in rats and rabbits.

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.

Nursing Mothers: It is not known whether topical ophthalmic administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in human milk. Systemic steroids appear in human milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. Caution should be exercised when Zylet is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

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

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, the incidence of ocular adverse events reported in greater than 10% of subjects 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 adverse events reported in approximately 14% of subjects was headache; all other non-ocular events 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. Other adverse reactions have not been reported; however, if topical ocular tobramycin is administered concomitantly with systemic aminoglycoside antibiotics, care should be taken to monitor the total serum concentration.

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.

DOSAGE AND ADMINISTRATION:
SHAKE VIGOROUSLY BEFORE USING.
Apply one or two drops of Zylet into the conjunctival sac of the affected eye(s) 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. Not more than 20 mL should be prescribed initially and the prescription should not be refilled without further evaluation as outlined in PRECAUTIONS above.

HOW SUPPLIED:
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:
2.5 mL (NDC 24208-358-25) in a 7.5 mL bottle
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.

KEEP OUT OF REACH OF CHILDREN

Rx only

Revised December 2004

Manufactured by:
Bausch & Lomb Incorporated
Tampa, FL 33637

Patent No. 4,996,335
Patent No. 5,540,930
Patent No. 5,747,061

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/s/

Lucious Lim
12/13/04 03:20:45 PM
MEDICAL OFFICER

William Boyd
12/13/04 03:26:32 PM
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Wiley Chambers
12/13/04 03:49:39 PM
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WD
6/30/04

Medical Officer's Review of NDA 21-675
120-Day Safety Update

Submission Date:	September 8, 2003
Received Date:	September 8, 2003
Review Completed:	June 29, 2004
Reviewer:	Lucious Lim, MD, MPH
Proposed Name:	Zylet (Loteprednol etabonate 0.5%/tobramycin 0.3% ophthalmic suspension)
Sponsor:	Bausch & Lomb 8500 Hidden River Parkway Tampa, FL 33637 (813) 866-2299 Contact: Julie Townsend, M.P.H.
Pharmacologic Category:	Corticosteroid/anti-infective fixed combination

The following statement concerning the 120-day safety update is contained in Volume 2.35 of the original NDA submission:

> This NDA includes final reports on all preclinical and clinical investigations conducted with loteprednol etabonate and tobramycin ophthalmic suspension, 0.5%/0.3%. Therefore, a four month safety update will not be necessary.

Reviewer's Comments:

Acceptable.

Lucious Lim, M.D., M.P.H.
Medical Officer

cc: NDA 21-675
HFD-550/Div Files
HFD-550/CSO/Rodriguez
HFD-550/CHEM/Tso

HFD-550/PHARM/Mukherjee
HFD-550/BIOPHARM/Chaurasia
HFD-550/MO/Lim
HFD-550/CTL/Boyd
HFD-550/Dep Div Director/Chambers

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/s/

Lucious Lim
7/1/04 05:41:17 PM
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Wiley Chambers
7/1/04 05:44:29 PM
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CLINICAL REVIEW of NDA 21-675

Original Application

Submitted:	September 8, 2003
Received:	September 8, 2003
Review completed:	May 12, 2004
Reviewer:	Lucious Lim, MD, MPH
Proposed Tradename:	Zylet
Established Name:	Loteprednol etabonate 0.5%/tobramycin 0.3% ophthalmic suspension
Sponsor:	Bausch & Lomb 8500 Hidden River Parkway Tampa, FL 33637 (813) 866-2299 Contact: Julie Townsend
Pharmacologic Category:	Corticosteroid/anti-infective combination
Proposed Indication:	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.
Dosage Form and Route of Administration:	Topical ocular ophthalmic suspension

Reviewer's Comments:

The italicized text within this review is intended to represent the comments and conclusions of this reviewer.

Table of Contents

Executive Summary

I. Recommendations

A. Recommendation on Approvability

NDA 21-675 is not recommended for approval. The submitted studies in NDA 21-675 are not sufficiently validated to establish efficacy (bioequivalence) for the use of Zylet (loteprednol etabonate 0.5%/tobramycin 0.3% ophthalmic suspension) in the treatment of 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.

B. Recommendation on Phase 4 Studies and/or Risk Management Steps

No additional Phase 4 studies are recommended. There are no additional recommended risk management steps for this product.

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

Zylet (loteprednol etabonate 0.5%/tobramycin 0.3% ophthalmic suspension) is a combination corticosteroid/anti-infective agent. It is an ophthalmic suspension for topical ocular administration. The corticosteroid component, Lotemax (loteprednol etabonate ophthalmic suspension 0.5%), is approved for the treatment of steroid responsive inflammatory conditions of the palpebral and bulbar conjunctiva, cornea, and anterior segment of the globe such as allergic conjunctivitis, acne rosacea, superficial punctuate keratitis, herpes zoster keratitis, iritis, cyclitis, selected infective conjunctivitides, when the inherent hazard of steroid use is accepted to obtain an advisable diminution in edema and inflammation. The anti-infective component, tobramycin ophthalmic solution USP 0.3% (Tobrex), is approved for the treatment of external infections of the eye and its adnexa caused my susceptible bacteria. Zylet (LET) is targeted for the treatment of 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.

B. Efficacy

The submitted studies in NDA 21-675 are not sufficiently validated to establish efficacy (bioequivalence) for the use of Zylet (loteprednol etabonate 0.5%/tobramycin 0.3% ophthalmic suspension) in the treatment of 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 bioequivalence studies submitted in NDA 21-675 are not sufficient to establish bioequivalence of the steroid component of the drug product. The data should be adequately validated.

C. Safety

The submitted studies in NDA 21-675 demonstrate an acceptable safety profile with the use of LET for the treatment of 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.

D. Dosing

The dosing regimen proposed in NDA 21-675 is one or two drops into the conjunctival sac of the affected eye(s) 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.

E. Special Populations

No additional data on special populations are needed.

Clinical Review

I. Introduction and Background

A. Drug Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups

Zylet (loteprednol etabonate 0.5%/tobramycin 0.3% ophthalmic suspension) is a combination corticosteroid/anti-infective agent. It is an ophthalmic suspension for topical ocular administration. The sponsor's proposed indication is 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 proposed dosing regimen is as follows: One or two drops into the conjunctival sac of the affected eye(s) 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.

B. State of Armamentarium for Indication(s)

Zylet is a combination ocular corticosteroid/anti-infective agent. Loteprednol etabonate is the corticosteroid component, and tobramycin is the anti-infective component of the drug product. There are multiple combination steroid/anti-infective ophthalmic solutions, suspensions, and ointments approved in the United States for use in the treatment of 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. Several of these combination products also are available generically.

C. Important Milestones in Product Development

There were no important milestones in the development of this product.

D. Other Relevant Information

The NDA for this combination product is submitted as a 505(b)(2) application. This NDA cross-references Bausch & Lomb's NDA 20-583, NDA 20-803, and ANDA 64-052, and Falcon's NDA 50-541 in support of the NDA. Loteprednol etabonate ophthalmic suspension 0.5% (Lotemax, NDA 20-583) is approved for the treatment of steroid responsive inflammatory conditions of the palpebral and bulbar conjunctiva, cornea and anterior segment of the globe such as allergic conjunctivitis, acne rosacea, superficial punctuate keratitis, herpes zoster keratitis, iritis, cyclitis, selected infective conjunctivitides, when the inherent hazard of steroid use is accepted to obtain an advisable diminution in edema and inflammation. Loteprednol etabonate ophthalmic suspension 0.2% (Alrex, NDA 20-803) is approved for the temporary relief of the signs and symptoms of seasonal allergic conjunctivitis. Tobramycin ophthalmic solution 0.3% (Tobrex,

NDA 50-541) and tobramycin ophthalmic solution 0.3%, USP (ANDA 64-052) are approved for the treatment of external infections of the eye and its adnexa caused by susceptible bacteria.

E. Important Issues with Pharmacologically Related Agents

There are no safety and effectiveness concerns associated with agents in this pharmacologic class.

II. Clinically Relevant Findings From Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews

Drug Product Composition

Ingredient	Quantity (mg/ml)
Loteprednol etabonate.	5.0
Tobramycin, USP	3
Benzalkonium chloride solution NF,	
Edetate disodium dehydrate, USP	
Glycerin, USP,	
Povidone, USP	
Tyloxapol, USP	
Purified water, USP	
Sulfuric acid,	Adjust pH
Sodium hydroxide,	Adjust pH

— mg/mL of tobramycin raw material is equivalent to 3.00 mg/mL if tobramycin raw material potency is µg/mg ("as is").

— label excess

Regulatory Drug Product Specification

Specification	Limit
[redacted]	

Sterility	Meet USP
Preservative Effectiveness	Meet USP

*Performed at release

III. Human Pharmacokinetics and Pharmacodynamics

A. Pharmacokinetics

The bioequivalence studies submitted in NDA 21-675 are not sufficient to establish bioequivalence of the steroid component of the drug product. The data should be adequately validated. See Clinical Pharmacology and Biopharmaceutics Review for detailed results.

B. Pharmacodynamics

The bioequivalence studies submitted in NDA 21-675 are not sufficient to establish bioequivalence of the steroid component of the drug product. The data should be adequately validated. See Clinical Pharmacology and Biopharmaceutics Review for detailed results.

IV. Description of Clinical Data and Sources

A. Overall Data

Five clinical studies and one microbial kill rate study are submitted in NDA 21-675. The clinical studies include two safety studies (studies 358-002 and 358-003), one clinical pharmacology study in sensitive volunteers (study 358-004), one pilot bioequivalence study (study 358-005), and one phase 3 bioequivalence study (study 358-006). The two safety studies, safety data from the other three submitted clinical studies, and *in-vitro* microbial kill rate study are evaluated in this Medical Officer's review. See Clinical Pharmacology and Biopharmaceutics Review for detailed results of Studies 358-004, 358-005, and 358-006. Study 358-006 and the microbial kill rate study are the primary support of efficacy (bioequivalence). Studies 358-002, 358-003, 358-004, and 358-005 contribute to the safety database.

B. Tables Listing the Clinical Trials

Table 1 – Description of Data Sources

Protocol Number	Study Design	Treatment Duration	Patient Population	Treatment Groups	Dosing	No. Sites	No. Subjects Randomized/ Completed	Status
Phase 1 Studies								
Safety and tolerability 358-002	Single-center, randomized, double-masked, paired group, Vehicle -controlled	14 days	Healthy adult volunteers	LET[1] Vehicle	1 drop one eye QID 1 drop other eye QID	1 (U.S.)	20/20	Completed
Safety 358-003	Single-center, randomized, double-masked, parallel group, Vehicle -controlled	42 days	Healthy adults volunteers	LET[1] Vehicle	1 drop QID	1 (U.S.)	168/158 (1:1)	Completed
Phase 2 Study								
Pilot pharmacokinetic (bioequivalence) 358-005	Single-center, randomized, masked, parallel group, Vehicle -controlled	1 day	Subjects undergoing cataract surgery	LET[1] LE[2] Placebo	2 drops or 4 drops 20 or 40 minutes prior to aqueous humor extraction	2 (U.S.)	68/68 (21:42:5)	Completed
Phase 3 Studies								
Conjunctival Provocation Test (clinical bioequivalence) 358-004	Single-center, randomized, double-masked, paired group, Vehicle -controlled	2 - 14 days	Sensitive healthy adult volunteers	LET[1] LE[2]	1 drop QID	1 (U.S.)	161/141	Completed
Pharmacokinetic (bioequivalence) 358-006	Multi-center, randomized, double-masked, parallel group, Vehicle -controlled	1 day	Subjects undergoing cataract surgery	LET[1] LE[2]	4 drops over 10 minute period 40 or 60 minutes prior to aqueous humor extraction	25 (U.S.)	2788/2700 (1:1)	Completed
Clinical Microbiology								
Addendum to "*In-Vitro*" microbial kill rate study: 06-5-97				LET[1] LE[2]				Completed

[1] loteprednol etabonate 0.5%/tobramycin ophthalmic suspension [2]loteprednol etabonate 0.5% ophthalmic suspension

C. **Postmarketing Experience**
No post-marketing data are available for this combination corticosteroid/anti-infection agent.

D. **Literature Review**
There is no data in the published literature pertinent to the review of this submission.

V. Clinical Review Methods

A. **How the Review was Conducted**
This medical officer's review evaluated each of the five studies separately.

B. **Overview of Materials Consulted in Review**
The submission is submitted in paper CTD format.

C. **Overview of Methods Used to Evaluate Data Quality and Integrity**
The Division of Scientific Investigations audited the analytical portion of study 358-006 (phase 3 bioequivalence study conducted to analyze loteprednol levels in the aqueous humor of study subjects). The audit identified multiple FDA Form 483 objectionable items e.g., failure of the analytical report to accurately reflect the source data and unacceptable data from multiple runs. The integrity of the bioequivalence dataset from study 358-006 submitted in NDA 21-675 in support of bioequivalence of the steroid component of the drug product is now in question. The dataset from study 358-006 is not acceptable without adequate validation of the data.

D. **Were Trials Conducted in Accordance with Accepted Ethical Standards**
There is no evidence to indicate that the trials were not conducted in accordance with accepted ethical standards.

E. **Evaluation of Financial Disclosure**
Financial disclosure statements are submitted. There is no evidence to indicate that participation of the investigator who has financial arrangements with applicant affected the integrity of the findings.

VI. Integrated Review of Efficacy

A. **Brief Statement of Conclusions**
The submitted studies in NDA 21-675 are not sufficient to establish efficacy (bioequivalence) for the use of Zylet (loteprednol etabonate 0.5%/tobramycin 0.3% ophthalmic suspension) in the treatment of 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.

B. General Approach to Review of the Efficacy of the Drug

The efficacy database consist of one pilot bioequivalence study (study 358-005) and one phase 3 bioequivalence study (study 358-006) in patients undergoing cataract surgery and one *in-vitro* microbial kill rate study.

C. Detailed Review of Trials by Indication

Proposed Indication: 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

Clinical Microbiology **Addendum to "*In-Vitro*" Microbial Kill Rate Study: 6/5/97**

Title: Comparison of "*In-Vitro*" Microbial Kill Rates: Loteprednol Etabonate and Tobramycin Ophthalmic Suspension, 0.5%/0.3% Compared to Tobramycin Ophthalmic Solution, USP, 0.3% (tobramycin)

Study Design: Each product (LET and tobramycin) and a control (sterile saline) were challenged with the test organisms listed in the USP Preservative Effectiveness Test and the organisms listed in the packaged insert of tobramycin ophthalmic solution. The organisms include:

S. aureus, P. aeruginosa, E. coli, S. epidermidis, S. pyogenes, S. mutans, S. pneumoniae, Klebsiella pneumoniae, Enterobacter aerogenes, Proteus mirabilis, Proteus vulgaris, Morganella morganii, H. influenzae, H. aegyptius, Moraxella lacunata, Acinebacter calcoaceticus, Nisesseria cinerea, and Nisseria elongate.

Colony counts were performed at time 0, 30 minutes, and 60 minutes.

Results: The negative control group (sterile saline) showed recovery values nearly equivalent to the initial inoculum at all time periods. Each of the active agents, LET and tobramycin demonstrate effective and equivalent kill rates. For each organism, the colony count is zero by 30 minutes and remained at zero at 60 minutes for each product.

Recovery Rates for Negative Control (saline)

		% Recovery		
Organism ATCC Number	Initial Inoculum (CFU/mL)	0 Minute (%)	30 Minutes (%)	60 Minutes (%)
S. aureus 6538	1.1×10^5	88	98	94
S. aureus 11632	6.5×10^5	86	88	88
S. aureus 13301	3.8×10^5	86	86	82
P. aeruginosa 9027	2.6×10^5	94	94	94
E. coli 8739	4.6×10^5	93	93	95

S. epidermidis 12228	3.1×10^5	87	84	84
S. pyogenes 49399	1.0×10^5	98	80	80
S. mutans 25175	3.8×10^5	93	88	82
S. pneumoniae 33400	1.5×10^5	88	81	81
K. pneumoniae 13883	1.8×10^5	94	98	98
E. aerogenes 13048	2.2×10^5	89	87	83
P. mirabilis 29906	5.5×10^5	89	91	88
P. vulgaris 13315	2.1×10^5	98	87	83
M. morganii 25830	6.5×10^5	98	100	98
H. influenzae 33391	1.0×10^5	84	98	80
H. aegyptius 11116	1.3×10^5	102	86	88
M. lacunata 17970	1.8×10^5	85	96	81
A. calcoaceticus 23055	7.5×10^5	85	85	85
N. cinerea 14685	5.5×10^5	93	88	88
N. elongate 25295	2.1×10^5	111	104	98

Recovery Rates for LET

		% Recovery		
Organism ATCC Number	Initial Inoculum (CFU/mL)	0 Minute (%)	30 Minutes (%)	60 Minutes (%)
S. aureus 6538	1.1×10^5	0	0	0
S. aureus 11632	6.5×10^5	0	0	0
S. aureus 13301	3.8×10^5	0	0	0
P. aeruginosa 9027	2.6×10^5	0	0	0
E. coli 8739	4.6×10^5	0	0	0
S. epidermidis 12228	3.1×10^5	0	0	0
S. pyogenes 49399	1.0×10^5	90	0	0
S. mutans 25175	3.8×10^5	68	0	0
S. pneumoniae 33400	1.5×10^5	0	0	0
K. pneumoniae 13883	1.8×10^5	0	0	0
E. aerogenes 13048	2.2×10^5	0	0	0
P. mirabilis 29906	5.5×10^5	0	0	0
P. vulgaris 13315	2.1×10^5	0	0	0
M. morganii 25830	6.5×10^5	0	0	0
H. influenzae 33391	1.0×10^5	84	0	0
H. aegyptius 11116	1.3×10^5	71	0	0
M. lacunata 17970	1.8×10^5	0	0	0
A. calcoaceticus 23055	7.5×10^5	0	0	0
N. cinerea 14685	5.5×10^5	0	0	0
N. elongate 25295	2.1×10^5	0	0	0

Recovery Rates for Tobramycin

		% Recovery		
Organism ATCC Number	Initial Inoculum (CFU/mL)	0 Minute (%)	30 Minutes (%)	60 Minutes (%)
S. aureus 6538	1.1×10^5	0	0	0
S. aureus 11632	6.5×10^5	0	0	0
S. aureus 13301	3.8×10^5	0	0	0
P. aeruginosa 9027	2.6×10^5	0	0	0

E. coli 8739	4.6×10^5	0	0	0
S. epidermidis 12228	3.1×10^5	0	0	0
S. pyogenes 49399	1.0×10^5	94	0	0
S. mutans 25175	3.8×10^5	64	0	0
S. pneumoniae 33400	1.5×10^5	0	0	0
K. pneumoniae 13883	1.8×10^5	0	0	0
E. aerogenes 13048	2.2×10^5	0	0	0
P. mirabilis 29906	5.5×10^5	0	0	0
P. vulgaris 13315	2.1×10^5	0	0	0
M. morganii 25830	6.5×10^5	0	0	0
H. influenzae 33391	1.0×10^5	46	0	0
H. aegyptius 11116	1.3×10^5	47	0	0
M. lacunata 17970	1.8×10^5	0	0	0
A. calcoaceticus 23055	7.5×10^5	0	0	0
N. cinerea 14685	5.5×10^5	0	0	0
N. elongate 25295	2.1×10^5	0	0	0

D. Efficacy Conclusions

The submitted studies in NDA 21-675 are not sufficiently validated to establish efficacy (bioequivalence) for the use of Zylet (loteprednol etabonate 0.5%/tobramycin 0.3% ophthalmic suspension) in the treatment of 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 bioequivalence studies submitted in NDA 21-675 are not sufficient to establish bioequivalence of the steroid component of the drug product. The data should be adequately validated.

VII. Integrated Review of Safety

A. Brief Statement of Conclusions

The submitted studies in NDA 21-675 demonstrate an acceptable safety profile with the use of LET for the treatment of 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.

B. Description of Patient Exposure

The safety database consists of 1,650 subjects from five clinical trials (protocols 358-002, 358-003, 358-004, 358-005, and 358-006):1,410 subjects undergoing cataract surgery and 240 healthy adult volunteers.

C. Methods and Specific Findings of Safety Review

The safety database consists of data from five clinical trials, protocols 358-002, 358-003, 358-004, 358-005, and 358-006. Protocol 358-005 did not report any adverse events.

Study #1 Protocol No. 358-002

Clinical Review Section

Title: A Randomized, Double-Masked, Placebo-Controlled, Safety and Tolerance Evaluation of Loteprednol Etabonate and Tobramycin Ophthalmic Suspension, 0.5%/0.3% Administered Four Times Daily for 14 Days in Healthy Volunteers

Safety

Subject Disposition and Demographics

Twenty subjects enrolled in the study and all completed the study.

Summary of Demographics

Variable	All subjects
N	20
Age (mean ± s.d., range)	40.6 ± 8.4 (23-54)
Sex:	
Male	5 (25%)
Female	15 (75%)
Race:	
Caucasian	20 (100%)
Iris Color:	
Brown	8 (40%)
Hazel	5 (25%)
Green	2 (10%)
Blue	5 (25%)

Adverse Events

Frequency and Incidence of Ocular and Non-ocular Adverse Events Occurring at Rates 1% and Greater

Coded Adverse Event	**Subjects reporting (N=20)**		
	One eye only		**Both eyes**
	LET (N=20)	**Vehicle (N=20)**	
	N (%)	N (%)	
OCULAR			
Blurred vision upon drop instillation	1 (5.0)		
Conjunctivitis	1 (5.0)		
Crusty debris			1 (5.0)
Dry eye		2 (10.0)	
Irritable sensation		1 (5.0)	
Itchy eye		1 (5.0)	
Mild ocular ache		1 (5.0)	
Scratchy		1 (5.0)	
Sticky eye		1 (5.0)	
Sting/burn upon instillation	7 (35.0)		
	Subjects reporting (N=20)		

NON-OCULAR	
Cold symptoms	2 (10.0)
Dry throat	1 (5.0)
Facial skin blemishes	1 (5.0)
Sinus headache	1 (5.0)

Visual Acuity

All subjects had 20/20 Snellen visual acuity at baseline and post-baseline visits.

Intraocular Pressure

No clinically significant differences between treatments (eyes) were observed at any visit.

Mean IOP from Baseline to Final Visit

Visit/Day	LET			Vehicle		
	N	Mean	S.D.	N	Mean	S.D.
1/0	20	15.0	2.5	20	15.3	2.4
2/1 (pre-Rx)	20	14.4	2.1	20	14.8	2.5
2/1 (post-Rx)	20	14.5	2.1	20	14.0	2.2
3/3	20	14.8	2.3	20	14.2	2.2
4/7	19	14.6	2.1	19	14.4	2.3
5/14 (final visit)	20	15.1	1.9	20	14.3	1.8

Ocular Comfort

Ocular comfort was measured using a 100 mm visual analog scale, with a higher score indicating greater comfort.

No clinically significant differences between treatments (eyes) were observed at any visit.

Biomicroscopy

No clinically significant change in slit lamp findings between treatments (eyes) were observed.

Study #2 **Protocol No. 358-003**

Title A Randomized, Double-Masked, Placebo-Controlled, Parallel Group, Safety Evaluation of Loteprednol Etabonate and Tobramycin Ophthalmic Suspension, 0.5%/0.3% Administered Four Times Daily for 6 Weeks in Healthy Volunteers

Safety

Subject Disposition and Demographics

One hundred sixty-eight (168) subjects enrolled in the study and 158 subjects completed the study.

Subject Disposition

	Number of Subjects		
	LET N (%)	Vehicle N (%)	Total N (%)
Randomized	112	56	168
Discontinued prematurely	9 (8.0)	1(1.8)	10 (6.0)
Included in safety evaluations	103 (92.0)	55 (98.2)	158 (94.0)

Discontinued Patients and Reasons

Subject number	Treatment	Day	Reason
008	LET	29	Subject planned out of town trip and could not continue.
060	LET	29	Adverse event - elevated IOP
075	LET	30	Adverse event - elevated IOP
091	LET	14	Adverse event - conjunctival abrasion
140	LET	7	Adverse event - corneal epithelial deposits. Possible viral etiology.
142	LET	15	Adverse event - light sensitivity
145	LET	29	Adverse event - elevated IOP
152	LET	33	Adverse event - redness, swollen lids & blurred vision
155	LET	28	Non-compliance – visit attendance
156	Vehicle	28	Adverse event – elevated IOP

Summary of Demographics

Variable	LET	Vehicle	p-value[1]	All subjects
N	112	56	0.2008	168
Age: N (%)				
Mean ± s.d. (range)	37.0 ± 11.4 (18-68)	40.8 ± 9.8 (18-60)		38.3 ± 11.0 (18-68)
< 40 years	65 (58%)	24 (43%)		89 (53%)
≥ 40 years	47 (42%)	32 (57%)		79 (47%)
SEX: N (%)			0.385	
Male	27 (24%)	17 (30%)		44 (26%)
Female	85 (76%)	39 (70%0		124 (74%)
RACE: N (%)			0.096	
Caucasian	30 (27%)	25 (45%)		55 (33%)
Black	6 (5%)	1 (2%)		7 (4%)
Hispanic	75 (67%)	30 (54%)		105 (63%)
American Indian	1 (1%)	0 (0)		1 (1%)

[1]P-value: for age, t-test, for sex and race, by Chi-square.

Adverse Events

Clinical Review Section

Frequency and Incidence of Ocular and Non-ocular Adverse Events
Occurring at Rates 1% and Greater

Coded Adverse Event	LET (N=112)	Vehicle (N=56)
	N (%)	N (%)
OCULAR		
Injection	23 (21.0)	16 (29.0)
Keratitis	14 (13.0)	10 (18.0)
Increased IOP	11 (10.0)	2 (4.0)
Burn/sting on instillation	10 (9.0)	2 (4.0)
Blurred vision	5 (4.0)	
Decreased visual acuity	3 (3.0)	
Discharge	3 (3.0)	
Itching	4 (4.0)	2 (4.0)
Lacrimation disorder	4 (4.0)	
Eye irritation	2 (2.0)	2 (4.0)
Photophobia	2 (2.0)	
Abnormal vision	1 (1.0)	1 (2.0)
Corneal deposits	1 (1.0)	
Eye disorder	1 (1.0)	
Eye pain	1 (1.0)	
Eyelid abnormality	1 (1.0)	1 (2.0)
Papilla	1 (1.0)	
Eye discomfort		1 (2.0)
Dry eyes		1 (2.0)
Foreign body sensation		3 (5.0)
NON-OCULAR		
Body as a Whole		
Headache	16 (14.0)	6 (11.0)
Accidental injury	1 (1.0)	
Pain	2 (2.0)	2 (4.0)
Cold, common	1 (1.0)	1 (2.0)
Pain, lower extremities	1 (1.0)	
Allergic reaction		1 (2.0)
Chest pain		1 (2.0)
Flu syndrome		1 (2.0)
Digestive System		
Periodontal abscess	1 (1.0)	
Hemolytic/Lymphatic System		
Leukocytosis	1 (1.0)	
Metabolic/Nutritional System		
Hyperglycemia	5 (4.0)	
Increased creatine phosphokinase	2 (2.0)	
Musculoskeletal System		
Myalgia	1 (1.0)	1 (2.0)
Nervous System		
Somnolence	1 (1.0)	1 (2.0)
Hyperesthesia		1 (2.0)
Respiratory System		
Sinusitis	4 (4.0)	2 (4.0)

Coded Adverse Event	LET (N=112)	Vehicle (N=56)
Pharyngitis	3 (3.0)	1 (2.0)
Rhinitis	3 (3.0)	2 (4.0)
Laryngitis	1 (1.0)	
Asthma		1 (2.0)
Skin and Appendages		
Alopecia	1 (1.0)	
Special Senses		
Ear pain	1 (1.0)	
Urogenital System		
Dysmenorrhea	2 (2.0)	1 (2.0)
Breast pain	1 (1.0)	
Unintended pregnancy	1 (1.0)	
Vaginitis	1 (1.0)	

Note: A subject may have more than one event (e.g., cold symptoms AND dry throat)

Intraocular Pressure

Mean IOP from Baseline to Final Visit

Visit/Day	LET			Vehicle		
	N	Mean	S.D.	N	Mean	S.D.
1/0	112	15.5	2.2	56	15.5	2.5
2/3	112	15.9	2.3	56	15.5	2.1
3/7	111	16.4	2.3	56	15.9	2.4
4/14	109	15.6	2.1	56	15.4	1.9
5/28	108	17.1	2.8	56	16.5	2.6
6/42	103	15.4	1.8	55	15.3	1.9
Final visit	112	15.7	2.5	56	15.5	2.3

All four subjects with IOP increase of ≥ 10 mmHg from baseline were from the LET treatment group.

IOP: Subjects with increase of ≥ 10 mmHg from baseline (either eye)

			Observed		Change from baseline	
Treatment	Subject No.	Visit (Day)	OD	OS	OD	OS
LET	60	29	26	30	7	12
		Final	26	30	7	12
LET	75	28	25	26	10	11
LET	79	28	23	24	11	12
LET	145	29	28	30	11	13
		Final	28	30	11	13

Visual Acuity

Change in Visual Acuity from Baseline to Final Visit

	Treatment Group

Line Changes	LET N (%)		Vehicle N (%)	
	OD	OS	OD	OS
N	112 (100.0)	112 (100.0)	56 (100.0)	56 (100.0)
≥ 3 lines loss				
2+ line loss	5 (4.5)	4 (3.6)	2 (3.6)	
1 line loss	19 (17.0)	22 (19.6)	10 (17.0)	8 (14.3)
No Change	62 (55.4)	65 (58.0)	29 (51.8)	29 (51.8)
1 line gain	24 (21.4)	15 (13.4)	13 (23.2)	12 (21.4)
2 line gain	1 (0.9)	6 (5.4)	2 (3.6)	7 (12.5)
≥ 3 lines gain	1 (0.9)			

Biomicroscopy

No clinically significant change from baseline for slit lamp findings was observed among the treatment groups.

Ophthalmoscopy

No clinically significant change from baseline for cup/disk ratio and fundus examination findings was observed among the treatment groups.

Clinical Laboratory Evaluation

No clinically significant change from baseline for laboratory values (hematology and blood chemistry) was observed among the treatment groups.

Study #3 **Protocol No. 358-004**

Title A Randomized, Double-Masked, Placebo-Controlled Comparison of the Clinical Bioequivalence of Bausch & Lomb Pharmaceuticals, Inc. Loteprednol Etabonate and Tobramycin Ophthalmic Suspension, 0.5%/0.3% Compared to Lotemax in Volunteers Exposed to Allergen Challenge

Safety

Subject Disposition and Demographics

One hundred sixty-one (161) subjects enrolled in the study and 141 subjects completed the study.

Subject Disposition

	Number of Subjects									
	LET/Vehicle			LE[1]/Vehicle			LET/LE			Total
	2D[2]	5D[3]	14D[4]	2D	5D	14D	2D	5D	14D	
Randomized	18	18	18	18	18	17	18	18	18	161
Discontinued prematurely	3	3	2		4	3	2	3		20
Completed	15	15	16	18	14	14	16	15	18	141

Clinical Review Section

[1]LE=Lotemax [2]2D=2 days [3]5D=5 days [4]14D=14 days

Discontinued Patients and Reasons

Subject number	Treatment	Loading Regimen/Visit	Reason
101-035	Vehicle/LET	5D/3	Disallowed medication
101-039	LET/LE	2D/3	Disallowed medication
101-058	LET/LE	5D/3	Disallowed medication IOP
101-043	LE/LET	5D/2	Lost to F/U
101-018	Vehicle/LE	14D/3	Adverse event – burning w/ instillation of study drug OU
101-061	Vehicle/LET	14D/2	Adverse event - burning w/ instillation of study drug OU
101-088	LET/Vehicle	5D/3	Adverse event - sinusitis
101-102	Vehicle/LE	5D/3	Adverse event – Flu symptoms
101-115	LET/Vehicle	2D/2	Adverse event – Flu symptoms
101-117	LET/Vehicle	14D/3	Adverse event – Muscle soreness, blurred vision
101-127	LET/Vehicle	5D/2	Adverse event - corneal blister
101-016	LE/Vehicle	5D/2	Other – subject missed visit 3
101-034	Vehicle/LET	2D/2	Other – subject missed visit 3
101-068	LET/LE	2D/2	Other – family death
101-082	LE/Vehicle	5D/2	Other – family emergency
101-092	Vehicle/LE	14D/2	Other – subject missed visit 3
101-116	Vehicle/LE	14D/2	Other - subject missed visit 3
101-135	LET/LE	5D/2	Other- subject missed visit 3
101-141	Vehicle/LET	2D/3	Other – subject decided to leave due to adverse weather
101-149	Vehicle/LE	5D/2	Other – subject missed visit 3

Adverse Events

Frequency and Incidence of Ocular and Non-ocular Adverse Events Occurring at Rates 1% and Greater

Coded Adverse Event	LET (N=100)	LE (N=100)	Vehicle (N=100)
	N (%)	N (%)	N (%)
OCULAR			
Burn/sting, eye, on instillation	2 (2.0)	2 (2.0)	3 (3.0)
Eyelid abnormality	1 (1.0)		
IOP increased	1 (1.0)	3 (3.0)	1 (1.0)
Lacrimation disorder	1 (1.0)		
Eye pain			1 (1.0)
Eye/vision, blurred		1 (1.0)	1 (1.0)
Hemorrhage, conjunctival		1 (1.0)	
Injection			1 (1.0)
Itching			1 (1.0)
Visual acuity decreased			1 (1.0)
NON-OCULAR			
Body as a Whole			
Cold, common	2 (2.0)	3 (3.0)	3 (3.0)

Headache	2 (2.0)	1 (1.0)	1 (1.0)
Back pain	1 (1.0)		1 (1.0)
Infection	1 (1.0)	1 (1.0)	
Myalgia	1 (1.0)		1 (1.0)
Pain	1 (1.0)	1 (1.0)	
Stiff neck	1 (1.0)		1 (1.0)
Allergic reaction		1 (1.0)	1 (1.0)
Flu syndrome		2 (2.0)	2 (2.0)
Respiratory System			
Sinusitis	1 (1.0)	1 (1.0)	2 (2.0)
Bronchitis		1 (1.0)	1 (1.0)
Skin and Appendages			
Rash	1 (1.0)	2 (2.0)	1 (1.0)
Special Senses			
Ear disorder	1 (1.0)	1 (1.0)	
Otitis media		1 (1.0)	1 (1.0)

Intraocular Pressure

No clinically significant change from baseline in intraocular pressure was observed among the treatment groups.

Visual Acuity

Change in Visual Acuity from
Baseline to Final Visit

	Treatment		
Line Changes	LET N (%)	LE N (%)	Vehicle N (%)
N	101 (100.0)	100 (100.0)	98 (100.0)
≥ 3 lines loss			1 (1.0)
2+ line loss	5 (5.0)	12 (12.0)	10 (10.1)
1 line loss	38 (37.6)	37 (37.0)	32 (32.3)
No Change	50 (49.5)	41 (41.0)	49 (49.5)
1 line gain	6 (5.9)	8 (8.0)	5 (5.1)
2 line gain	2 (2.0)	2 (2.0)	
≥ 3 lines gain			2 (2.0)

Biomicroscopy

No clinically significant change from baseline for slit to lamp findings was observed among the treatment groups.

Study #4 **Protocol No. 358-005**

Title A Pilot, Randomized, Single-Center Comparison of the Aqueous Humor Concentration of Loteprednol Etabonate Following Administration of Bausch & Lomb Pharmaceuticals, Inc. Loteprednol Etabonate and Tobramycin Ophthalmic

Suspension, 0.5%/0.3% Compared to Lotemax (Loteprednol Etabonate Ophthalmic Suspension, 0.5%) During Routine Cataract Surgery

Safety

Subject Disposition
Sixty eight (68) subjects enrolled in the study and all subjects completed the study.

Subject Disposition

	Treatment Group						
	LE/20 N (%)	LE/40A N (%)	LET/20 N (%)	LET/40 N (%)	LE/40B N (%)	None N (%)	Total N (%)
Enrolled	11 (100.0)	10 (100.0)	10 (100.0)	11 (100.0)	21 (100.0)	5 (100.0)	68 (100.0)
Completed	11 (100.0)	10 (100.0)	10 (100.0)	11 (100.0)	21 (100.0)	5 (100.0)	68 (100.0)

LE/20=Lotemax treatment (2 instillationss) with a 20 minute sample. LE/40A=Lotemax treatment (2 drops) with a 40 minute sample. LET/20=LET treatment with a 20 minute sample. LET/40=LET treatment with a 40 minute sample. LE/40B=Lotemax treatment (4 instillations) with a 40 minute sample. None=No study medications.

Adverse Events

No adverse events were reported during the study period.

Visual Acuity

No post-baseline visual acuity measurements were performed.

Study #5 **Protocol No. 358-006**

Title A Randomized, Double-Masked, Multi-Center Comparison of the Aqueous Humor Concentration of Loteprednol Etabonate Following Administration of Bausch & Lomb Loteprednol Etabonate and Tobramycin Ophthalmic Suspension 0.5%/0.3% or Lotemax (Loteprednol Etabonate Ophthalmic Suspension, 0.5%) During Routine Cataract Surgery

Safety

Subject Disposition

Two thousand, seven hundred and eighty-eight (2788) subjects enrolled in the study and 2700 subjects completed the study.

Subject Disposition

	Treatment Group				
	LE/40 N (%)	LE/60 N (%)	LET/40 N (%)	LET/60 N (%)	Total N (%)

Enrolled	697 (100.0)	702 (100.0)	694 (100.0)	695 (100.0)	2788 (100.0)
Discontinued prematurely	21 (3.0)	24 (3.4)	23 (3.3)	20 (2.9)	88 (3.2)
Completed	676 (97.0)	678 (96.6)	671 (96.3)	675 (97.1)	2700 (96.8)

LE/40=Lotemax treatment with 40 minute sample. LX/60=Lotemax treatment with 60 minute sample. LET/40=LET treatment with 40 minute sample. LET/60=LET treatment with 60 minute sample.

Discontinued Patients and Reasons

Investigator Number	Subject Number	Treatment	Reason
105375	243	LE/40	Other – timing issues
105380	96	LET/40	Other – uncooperative patient and collection problems
108756	1399	LE/40	Other – timing issues
	1423	LE/60	Other – timing issues
	1426	LE/40	Other – timing issues
	2235	LET/40	Other – timing issues
	2245	LE/60	Other – timing issues
	3018	LET/60	Adverse event – elevated BP, HR, and blood glucose pre-op, secondary to not using hypertension medications
111265	1505	LE/40	Other – timing issues
116110	22	LE/60	Other – timing issues
	39	LE/60	Other – timing issues
	1449	LE/40	Other – collection problems
	2203	LET/40	Other – collection problems
116290	277	LET/40	Other – timing issues
	278	LET/60	Other – timing issues
	279	LE/40	Other – timing issues
117840	694	LET/60	Other – timing issues
122010	417	LE/60	Other – timing issues
122330	881	LET/40	Other – timing issues
	1292	LE/60	Other – collection problem
	1304	LET/40	Other – concomitant medication issues
123840	171	LE/40	Adverse event – intra-operative photophobia
	175	LE/40	Voluntarily withdrew consent – prior to receiving study medication
	189	LET/60	Other – collection problems
	190	LE/40	Other – timing issues
	200	LE/40	Other – timing issues
	201	LET/60	Other – timing issues
	205	LET/60	Other – timing issues
	1513	LE/40	Other – timing issues
	1530	LE/40	Other – timing issues
	1532	LET/60	Other – timing issues
	1533	LET/40	Other – timing issues
	1534	LE/40	Other – timing issues
	1543	LE/60	Other – timing issues
	2158	LE/60	Other – timing issues
	2160	LET/40	Other – timing issues
	2162	LET/60	Other – timing issues
	2171	LE/40	Other – timing issues
	2173	LE/60	Other – timing issues

Investigator Number	Subject Number	Treatment	Reason
	2498	LET/60	Other – timing issues
	9998	LE/60	Other – received incorrect study medication
129125	1120	LE/40	Other – timing issues
	1133	LET/60	Other – timing issues
	2381	LE/60	Other – timing issues
	2384	LET/40	Other – timing issues
130210	784	LE/60	Other – dosing error and concomitant medication issues
136800	2871	LET/40	Other – collection problems
140750	464	LE/40	Other – collection problems
	1656	LET/60	Other – timing issues
	1666	LE/60	Other – timing issues
	2490	LET/40	Other – collection problems
153325	334	LET/40	Other – timing issues
	354	LET/60	Other – timing issues
	357	LET/40	Other – timing issues
	358	LE/40	Other – timing issues
	360	LE/60	Other – timing issues
	365	LE/40	Other – timing issues
	366	LET/60	Other – timing issues
	367	LET/40	Other – visual acuity did not meet enrollment criterion
	1813	LET/40	Other – timing issues
	1814	LE/60	Other – timing issues
	1815	LET/60	Other – timing issues
	3124	LET/40	Other – timing issues
	3126	LE/60	Other – timing issues
	3128	LE/40	Other – timing issues
153355	1225	LE/60	Other – timing issues and concomitant medication issues
	1226	LET/40	Other – timing issues
	1683	LET/60	Other – timing issues
	1706	LET/60	Other – timing issues
	2602	LET/40	Other – timing issues
	2603	LE/60	Other – timing issues
	2604	LET/60	Other – timing issues
	2633	LET/60	Other – timing issues
153380	55	LET/40	Other – study medication not given due to information problem
	88	LE/40	Other – timing issues
	613	LE/60	Other – timing issues
	1553	LET/40	Other – timing issues
	1580	LET/60	Other – timing issues
	1583	LE/60	Other – surgery cancelled due to cardiac rhythm concern
	1839	LET/60	Other – timing issues
	2526	LE/60	Other – timing issues
158773	517	LET/40	Other – timing issues
	518	LE/40	Other – timing issues
	519	LE/60	Other – timing issues
	1977	LET/40	Other – visual acuity did not meet enrollment criterion and timing issues
	2542	LE/40	Other – timing issues
253847	2958	LET/40	Other – timing issues

Investigator Number	Subject Number	Treatment	Reason
	2960	LE/60	Other – collection problems

Adverse Events

Frequency and Incidence of Ocular and Non-ocular Adverse Events
Occurring at Rates 1% and Greater

Coded Adverse Event	LE (N=1396)	LET (N=1388)
	N (%)	N (%)
OCULAR		
Inflammation, anterior chamber	491 (35.2)	495 (35.7)
Edema, corneal	194 (13.9)	217 (15.6)
Eye/vision, blurred	134 (9.6)	149 (10.7)
Corneal striae	134 (9.6)	142 (10.2)
Visual acuity decreased	138 (9.9)	135 (9.7)
Foreign body sensation	115 (8.2)	122 (8.8)
Corneal abnormality	137 (9.8)	120 (8.6)
Intraocular pressure, increased	104 (7.4)	96 (6.9)
Eye pain	81 (5.8)	89 (6.4)
Abnormal vision	92 (6.6)	82 (5.9)
Injection	76 (5.4)	77 (5.5)
Opacity, posterior capsule	72 (5.2)	60 (4.3)
Cataract surgery complication	49 (3.5)	46 (3.3)
Itching, eye	27 (1.9)	37 (2.7)
Vitreous disorder	39 (2.8)	37 (2.7)
Lacrimation disorder	32 (2.3)	36 (2.6)
Photophobia	15 (1.1)	26 (1.9)
Retinal disorder	28 (2.0)	23 (1.7)
Discomfort, eye	29 (2.1)	22 (1.6)
Dry eyes	16 (1.1)	22 (1.6)
Hemorrhage, conjunctival		21 (1.5)
Keratitis	20 (1.4)	20 (1.4)
Eyelid abnormality	14 (1.0)	19 (1.4)
Eye disorder		18 (1.3)
Chromatopsia	22 (1.6)	17 (1.2)
Burning/stinging, eye, not on instillation		14 (1.0)
Macular edema	18 (1.3)	14 (1.0)
Irritation, eye	20 (1.4)	
NON-OCULAR		
Body as a Whole		
Headache	28 (2.0)	32 (2.3)
Digestive System		
Nausea	14 (1.0)	18 (1.3)

Visual Acuity

Change in Visual Acuity from
Baseline to Final Visit

Line Changes	Treatment Group	
	LE N (%)	LET N (%)
N	1256 (100.0)	1245 (100.0)
≥ 3 lines loss	43 (3.5)	50 (4.0)
2+ line loss	25 (2.0)	19 (1.5)
1 line loss	33 (2.6)	35 (2.8)
No Change	243 (19.3)	219 (17.6)
1 line gain	138 (11.0)	140 (11.2)
2 line gain	133 (10.6)	142 (11.4)
≥ 3 lines gain	641 (51.0)	640 (51.4)

D. Adequacy of Safety Testing

The safety database from five submitted clinical studies in NDA 21-675 is adequate.

E. Summary of Critical Safety Findings and Limitations of Data

LET is expected to be safe when used as proposed in the label.

VIII. Dosing, Regimen, and Administration Issues

The proposed dosing regimen is a modified version of the approved Lotemax labeling. It is recommended that LET's dosing regimen match the dosing regimen in Lotemax's labeling.

IX. Use in Special Populations

A. Evaluation of Sponsor's Gender Effects Analyses and Adequacy of Investigation

The primary support of efficacy are data from two bioequivalence studies and an *in-vitro* microbial kill rate study. The primary support of safety is data from five submitted clinical studies. No analyses on the effects of gender on safety and efficacy were performed.

B. Evaluation of Evidence for Age, Race, or Ethnicity Effects on Safety or Efficacy

The primary support of efficacy are data from two bioequivalence studies and an *in-vitro* microbial kill rate study. The primary support of safety is data from five submitted clinical studies. No analyses on the effects of age, and ethnicity on safety and efficacy were performed.

C. Evaluation of Pediatric Program

It is the agency's view that the drug product does not represent a meaningful therapeutic benefit over existing treatments for pediatric patients and is not likely to be used in a significant number of pediatric patients. A waiver for pediatric studies is recommended.

D. Comments on Data Available or Needed in Other Populations

No additional data in other special populations are needed.

X. Conclusions and Recommendations

A. Conclusions

The submitted studies in NDA 21-675 are not sufficiently validated to establish efficacy (bioequivalence) for the use of Zylet (loteprednol etabonate 0.5%/tobramycin 0.3% ophthalmic suspension) in the treatment of 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.

B. Recommendations

NDA 21-571 is not recommended for approval for the treatment of 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.

XI. Appendix

A. Other Relevant Materials

Summary of Frequency and Incidence of Ocular and Non-ocular Adverse Events Occurring at Rates 1% and Greater (Protocols 358-002, 358-003, 358-004, 358-006)

Appears This Way
On Original

Summary of Frequency and Incidence of Ocular and Non-ocular Adverse Events Occurring at Rates 1% and Greater
(Protocols 358-002, 358-003, 358-004, 358-006)

Coded Adverse Event	LET				LE		Vehicle		
Protocol	**358-002** (N=20)	**358-003** (N=112)	**358-004** (N=100)	**358-006** (N=1388)	**358-004** (N=100)	**358-006** (N=1396)	**358-002** (N=20)	**358-003** (N=56)	**358-004** (N=100)
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
OCULAR									
Abnormal vision		1 (1.0)		82 (5.9)		92 (6.6)		1 (2.0)	
Blurred vision		5 (4.0)		149 (10.7)	1 (1.0)	134 (9.6)			1 (1.0)
Blurred vision upon drop instillation	1 (5.0)								
Cataract surgery complication				46 (3.3)		49 (3.5)			
Chromatopsia				17 (1.2)		22 (1.6)			
Conjunctivitis	1 (5.0)								
Corneal abnormality				120 (8.6)		137 (9.8)			
Corneal deposits		1 (1.0)							
Corneal striae				142 (10.2)		134 (9.6)			
Crusty debris	1 (5.0)						1 (5.0)		
Decreased visual acuity		3 (3.0)		135 (9.7)		138 (9.9)			1 (1.0)
Discharge									
Discomfort, eye				22 (1.6)		29 (2.1)		1 (2.0)	
Dry eye				22 (1.6)		16 (1.1)	2 (10.0)	1 (2.0)	
Dysmenorrhea		2 (2.0)						1 (2.0)	
Ear pain		1 (1.0)							
Edema, corneal				217 (15.6)		194 (13.9)			
Eye disorder		1 (1.0)		18 (1.3)					
Eye pain		1 (1.0)		89 (6.4)		81 (5.8)			1 (1.0)
Eyelid abnormality		1 (1.0)	1 (1.0)	19 (1.4)		14 (1.0)		1 (2.0)	
Foreign body sensation				122 (8.8)		115 (8.2)		3 (5.0)	
Hemorrhage, conjunctival				21 (1.5)	1 (1.0)				
Increased IOP		11 (10.0)	1 (1.0)	96 (6.9)	3 (3.0)		104 (7.4)	2 (4.0)	1 (1.0)

Coded Adverse Event	LET				LE		Vehicle		
Protocol	**358-002** (N=20)	**358-003** (N=112)	**358-004** (N=100)	**358-006** (N=1388)	**358-004** (N=100)	**358-006** (N=1396)	**358-002** (N=20)	**358-003** (N=56)	**358-004** (N=100)
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Inflammation, anterior chamber				495 (35.7)		491 (35.2)			
Injection		23 (21.0)		77 (5.5)		76 (5.4)		16 (29.0)	1 (1.0)
Irritable sensation		2 (2.0)				10 (1.4)	1 (5.0)	2 (4.0)	
Itchy eye		4 (4.0)		37 (2.7)		27 (1.9)	1 (5.0)	2 (4.0)	
Keratitis		14 (13.0)		20 (1.4)		20 (1.4)		10 (18.0)	
Lacrimation disorder		4 (4.0)	1 (1.0)	36 (2.6)		32 (2.3)			
Macular edema				14 (1.0)		18 (1.3)			
Mild ocular ache							1 (5.0)		
Opacity, posterior capsule				60 (4.3)		72 (5.2)			
Papilla		1 (1.0)							
Photophobia		2 (2.0)		26 (1.9)		15 (1.1)			
Retinal disorder				23 (1.7)		28 (2.0)			
Scratchy							1 (5.0)		
Sticky eye							1 (5.0)		
Sting/burn upon instillation	7 (35.0)	10 (9.0)	2 (2.0)	14 (1.0)	2 (2.0)			2 (4.0)	3 (3.0)
Vitreous disorder				37 (2.7)		39 (2.8)			
NON-OCULAR									
Accidental injury		1 (1.0)							
Allergic reaction					1 (1.0)			1 (2.0)	1 (1.0)
Alopecia		1 (1.0)							
Asthma								1 (2.0)	
Back pain			1 (1.0)						1 (1.0)
Breast pain		1 (1.0)							
Bronchitis					1 (1.0)				1 (1.0)
Chest pain								1 (2.0)	
Cold symptoms	2 (10.0)	1 (1.0)	2 (2.0)		3 (3.0)		2 (10.0)	1 (2.0)	3 (3.0)
Dry throat	1 (5.0)						1 (5.0)		
Ear disorder			1 (1:0)		1 (1.0)				
Facial skin	1 (5.0)						1 (5.0)		

Coded Adverse Event	LET				LE		Vehicle		
Protocol	358-002 (N=20)	358-003 (N=112)	358-004 (N=100)	358-006 (N=1388)	358-004 (N=100)	358-006 (N=1396)	358-002 (N=20)	358-003 (N=56)	358-004 (N=100)
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Blemishes									
Flu syndrome					2 (2.0)			1 (2.0)	2 (2.0)
Headache, sinus	1 (5.0)						1 (5.0)		
Headache		16 (14.0)	2 (2.0)	32 (2.3)	1 (1.0)	28 (2.0)		6 (11.0)	1 1.0)
Hyperesthesia								1 (2.0)	
Hyperglycemia		5 (4.0)							
Increased creatine phosphokinase		2 (2.0)							
Infection			1 (1.0)		1 (1.0)				
Leukocytosis		1 (1.0)						1 (2.0)	
Myalgia		1 (1.0)	1 (1.0)						1 (1.0)
Nausea				18 (1.3)		14 (1.0)			
Otitis media					1 (1.0)				1 (1.0)
Pain		2 (2.0)	1 (1.0)		1 (1.0)			2 (4.0)	
Pain, lower extremities		1 (1.0)							
Periodontal abscess		1 (1.0)							
Pharyngitis		3 (3.0)						1 (2.0)	
Rash			1 (1.0)		2 (2.0)				1 (1.0)
Rhinitis		3 (3.0)						2 (4.0)	
Sinusitis		4 (4.0)	1 (1.0)		1 (1.0)			2 (4.0)	2 (2.0)
Somnolence		1 (1.0)						1 (2.0)	
Stiff neck		1 (1.0)							1 (1.0)
Unintended pregnancy		1 (1.0)							
Vaginitis		1 (1.0)							

B. Individual More Detailed Study Reviews (if performed)
None

C. Labeling

Reviewer recommended deletions are noted by and additions by underline within the review.

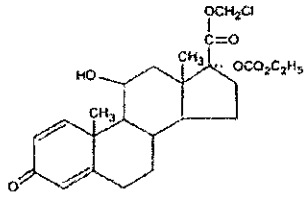
Zylet™
loteprednol etabonate 0.5% and tobramycin 0.3% ophthalmic suspension

Rx only

STERILE

DESCRIPTION:
Zylet (loteprednol etabonate and tobramycin ophthalmic suspension), is a sterile, multiple dose topical anti-inflammatory corticosteroid and antibiotic combination for ophthalmic use. Loteprenol etabonate is an amorphous solid and tobramycin is a white to off-white powder. The chemical structures of loteprednol etabonate and tobramycin are shown below.

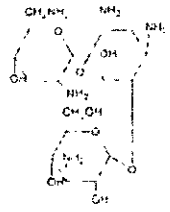
Loteprednol etabonate:



$C_{24}H_{31}ClO_7$ 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

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_____ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

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