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RESEARCH**

APPLICATION NUMBER:
200738Orig1s000

MEDICAL REVIEW(S)

Clinical Review #2
NDA 200738

Application Type	NDA
Application Number(s)	200738
Letter Date	1/21/11
Stamp Date	1/25/11
PDUFA Goal Date	7/25/11
Reviewer Name	Sonal D. Wadhwa, MD
Review Completion Date	4/12/11
Established Name	Loteprednol etabonate ophthalmic ointment, 0.5%
(Proposed) Trade Name	Lotemax
Therapeutic Class	Corticosteroid
Applicant	Bausch and Lomb
Priority Designation	S

Recommendation on Regulatory Action

NDA 200738 is recommended for approval for the treatment of post-operative inflammation and pain following ocular surgery with the labeling found in this review (package insert submitted 4/11/11 and carton/container labeling submitted 10/14/10).

NDA 200738 received a Complete Response Letter dated 10/20/10. The letter cited two deficiencies:

- 1) Manufacturing facilities for the drug substance are not in compliance with current good manufacturing practice. Please amend the application with facilities that are in compliance with current good manufacturing practice (cGMP) or notify us when all currently submitted facilities are in compliance with cGMPs.
- 2) The proposed controls for the drug product are inadequate to preserve the quality or stability of the drug product. Specifically, the wide acceptance criteria do not provide adequate control on dose uniformity. The acceptance criteria should be based on data from homogeneous samples at release with a narrower range than currently proposed. The dose uniformity test with appropriate acceptance criteria should be able to identify settling in samples during stability. When responding to this deficiency, please submit the complete data set from the stability studies.

These two deficiencies have been adequately addressed by the applicant.

8 Page(s) of draft labeling have been Withheld in Full as b4
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/s/

SONAL D WADHWA
04/13/2011

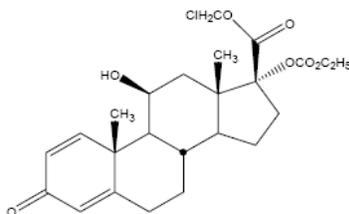
WILLIAM M BOYD
04/13/2011

Division Director Review for NDA 200738

Date	October 13, 2010
From	Wiley A. Chambers, M.D.
NDA #	200738
Applicant	Bausch & Lomb Incorporated
Date of Submission	December 23, 2009
PDUFA Goal Date	October 23, 2010
Type of Application	505(b)(1)
Name	Lotemax (loteprednol etabonate ophthalmic ointment) 0.5%
Dosage forms / Strength	Topical ophthalmic ointment
Proposed Indication(s)	Treatment of post-operative inflammation and pain following ocular surgery
Action:	Complete Response – Not approved

1. Introduction/Background

Loteprednol etabonate ophthalmic ointment (LE) is a sterile, topical, anti-inflammatory corticosteroid formulation. The drug product, developed by Bausch & Lomb (B&L), is an ophthalmic ointment containing 0.5% loteprednol etabonate. The drug is (b) (4) of white petrolatum and mineral oil.



Loteprednol etabonate has been marketed in the United States by Bausch & Lomb since 1998 as Lotemax (loteprednol etabonate ophthalmic suspension) 0.5% and Alrex (loteprednol etabonate ophthalmic suspension) 0.2% and marketed since 2005 in a fixed combination with tobramycin as Zylet (loteprednol etabonate and tobramycin ophthalmic suspension). The product development for loteprednol etabonate ophthalmic ointment, 0.5% was conducted under IND 32,432.

Ocular AEs generally associated with ophthalmic steroids include elevated IOP (which may be associated with optic nerve damage and visual acuity and field defects), posterior subcapsular cataract formation, secondary ocular infection from pathogens including herpes simplex, and perforation of the globe where there is thinning of the cornea or sclera.

2. CMC

The drug substance, loteprednol etabonate, is a white to off-white powder. It is insoluble in water. The chemical name is chloromethyl 17 α -[(ethoxycarbonyl)oxy]-11 β -hydroxy-3-oxoandrosta-1,4-diene-17 β -carboxylate. The molecular formula is C₂₄H₃₁ClO₇ and the molecular weight of loteprednol etabonate is 466.96. Loteprednol etabonate is the same drug substance as is currently used in Lotemax

Lotemax (loteprednol etabonate ophthalmic ointment), 0.5%

(loteprednol etabonate ophthalmic suspension 0.5%) (NDA 20-583). The drug substance is manufactured and (b) (4) DMF (b) (4) is referenced for drug substance information. The drug product, Lotemax (loteprednol etabonate ophthalmic ointment) 0.5%, will be manufactured at the facility in Tampa.

DESCRIPTION AND COMPOSITION OF THE DRUG PRODUCT:

Component	Reference to Quality Standard	Function	Concentration (mg/g)	% w/w
Sterile Loteprednol Etabonate	In-house	Active	5.0	0.5
Mineral Oil	USP	(b) (4)	(b) (4)	
White Petrolatum	USP	(b) (4)	(b) (4)	

Commercial drug product will be packaged as a nominal 3.5g fill in 3.5g tin tubes with pink LDPE caps. In addition, a physician’s sample size configuration consisting of a nominal 1g fill in 2g tin tubes with pink LDPE caps is also proposed. The average weight of one dose (a ½ inch ribbon) of ointment was determined to be 30.0 mg with a standard deviation of 6.6 mg. Individual ½ inch ribbons ranged in weight from 16.2 mg to 48.7 mg.

FACILITY INSPECTIONS

A site recommendation of “Withhold” was made by the Office of Compliance, since manufacturing facilities for the drug substance (b) (4) are not in compliance with current good manufacturing practice. Satisfactory resolution of this deficiency is required before this application may be approved.

PROPOSED SPECIFICATIONS:

Drug Product Specifications

Test	Analytical Procedure	Acceptance Criteria	
		Release	Shelf life
Description	Visual (PS-1008)	Off-white to yellowish homogeneous ointment	
Particulate Matter	Visual (PS-1013)	Essentially free of foreign particulate matter	Not applicable
Metal Particles	USP<751> (PS-1001)	(b) (4)	Not applicable
Particle Size Distribution	C-1812	(b) (4)	Not applicable
Identification A	C-1689 (HPLC)	The retention time for loteprednol etabonate peak in the sample corresponds to that of the standard	Not applicable
Identification B	C-1689 (UV)	The UV spectrum of the assay preparation exhibits its maximum at the same wavelength as that of the standard	Not applicable

Assay	C-1689 (HPLC)	95.0 – 105.0% of label claim	90.0–110.0% (b) (4)
Related Substances ^	C-1689 (HPLC)	(b) (4)	
		Total Chromatographic Related Substances	NMT (b) (4)
(b) (4)	C-1798 (HPLC)	NMT (b) (4)	
Dose Uniformity	C-1817 (HPLC)	Not Applicable	See below*
Leak Test	USP<771> (PS-1006)	Meets USP requirements	Not applicable
Minimum Fill	USP<755> (PS-1003)	Meets USP requirements	Not applicable
(b) (4)	C-1204 (b) (4)	NMT (b) (4)	
Sterility	USP <71> 24-T012 or B-1044	Meets USP requirements	
Endotoxin	Complies with USP <85> (72-156 or STP0046)	NMT (b) (4)	Not applicable

^ Any loteprednol etabonate synthetic process impurities, which are not also shown to be degradation products, would be controlled in the drug substance in accordance with ICH Q6A.

(b) (4)

(b) (4)

CMC determined that the proposed acceptance criterion for Dose Uniformity was not acceptable. The proposed acceptance criterion does not provide appropriate control on dose uniformity. The dose uniformity test with appropriate acceptance criteria should be able to identify settling in samples during stability.

3. Nonclinical Pharmacology/Toxicology

The nonclinical safety profile of loteprednol etabonate (LE) has been extensively evaluated as a 0.5% ophthalmic suspension under NDA 20-583 (approved March 1998). For the development of 0.5% loteprednol etabonate ophthalmic ointment, the sponsor has conducted 28-day ocular toxicity studies in rabbits and dogs. The study reports showed no significant toxicity findings except for the transient irregular aspect of ocular surface (in both treated and control groups) caused by the viscous consistency of the ointment vehicle. The current label for the marketed loteprednol etabonate (LE) states that LE was not genotoxic in a battery of genotoxicity tests. LE has been shown to be embryotoxic and teratogenic. No carcinogenic studies have been conducted for LE.

4. Clinical Pharmacology/Biopharmaceutics

Clinical pharmacokinetic studies were conducted during the development of Lotemax suspension and Zylet, and these data have been submitted previously with the corresponding NDAs for these products (NDA #20-583 and #50-804, respectively). No new clinical pharmacology data was presented in this

application. The pharmacokinetic data previously submitted addresses requirement for bioavailability outlined in 21 CFR 320.21.

5. Sterility Assurance

(b) (4)

The drug product is a sterile topical ophthalmic ointment in a multi-dose tube. A microbial ingress test was used to validate container closure integrity for the tin tubes. The study was performed using 3.5 g tubes with LDPE caps. Media-filled tubes were immersed in a suspension of *B. cepacia* (6.2×10^8 CFU/mL) for 20 minutes at room temperature. Following immersion, the test samples were subjected to 5 psi (above atmospheric) of pressure for 5 minutes followed by 5 minutes at 5 inches of mercury (vacuum). The test units were then incubated at $32.5 \pm 2.5^\circ\text{C}$ for 7 days. After incubation, the contents of the test units were examined for evidence of microbial growth. None of the test units or negative controls (not immersed in the microbial suspension) was positive for growth. The growth promotion units (inoculated with 10-100 CFU of *B. cepacia*) and the positive control units (breached units) were positive for microbial growth.

(b) (4)

The drug product was tested using USP <51> antimicrobial effectiveness testing. In addition to the 5 test organisms listed in USP <51>, four additional organisms were used in the test. The acceptance criteria were achieved for a USP Category 1 product (includes ophthalmic products).

6. Clinical/Statistical - Efficacy

Study 525: Inflammation Cleared Analysis (ITT Population)

	LE Ointment N=201	Vehicle N=199	P value
Day 3	10 (5%)	9 (5%)	0.8315
Day 8 – primary endpoint	48 (24%)	27 (14%)	0.0022
Day 15	84 (42%)	30 (15%)	<0.0001
Day 18	86 (43%)	39 (20%)	<0.0001

Study 526: Inflammation Cleared Analysis (ITT Population)

	LE Ointment N=203	Vehicle N=202	P value
Day 3	10 (5%)	9 (5%)	0.8020
Day 8 – primary endpoint	64 (31%)	23 (11%)	0.0001
Day 15	107 (53%)	42 (21%)	<0.0001
Day 18	100 (49%)	46 (23%)	<0.0001

Study 525: Mean ACR Count (ITT Population)

	Number of Subjects in LE Ointment	LE Ointment	Number of Subjects in Vehicle	Vehicle
Visit 1-Screening	201	0	199	0
Visit 3-POD#1 (sd)	201	3.7 (0.8)	199	3.8 (0.9)
Visit 4-POD #3 (sd)	200	2.7 (1.2)	196	3.3 (1.5)
Visit 5-POD #8 (sd)	199	1.6 (1.3)	195	3.0 (1.8)
Visit 6-POD #15 (sd)	199	1.1 (1.3)	195	2.8 (1.9)
Visit 7-POD #18 (sd)	200	1.2 (1.4)	195	2.7 (1.9)

Study 526: Mean ACR Count (ITT Population)

	Number of Subjects in LE Ointment	LE Ointment	Number of Subjects in Vehicle	Vehicle
Visit 1-Screening	203	0	202	0
Visit 3-POD#1 (sd)	203	3.7 (0.7)	202	3.7 (0.7)
Visit 4-POD #3 (sd)	202	2.5 (1.2)	202	3.1 (1.5)
Visit 5-POD #8 (sd)	201	1.5 (1.5)	201	2.9 (1.8)
Visit 6-POD #15 (sd)	200	1.0 (1.5)	201	2.6 (2.0)
Visit 7-POD #18 (sd)	201	1.1 (1.5)	199	2.6 (2.0)

Study 525: Pain Free Analysis (ITT Population)

	LE Ointment N=201	Vehicle N=199	P value
Day 3	148 (74%)	85 (43%)	<0.0001
Day 8	156 (78%)	90 (45%)	<0.0001
Day 15	152 (76%)	79 (40%)	<0.0001
Day 18	125 (62%)	64 (32%)	<0.0001

Study 526: Pain Free Analysis (ITT Population)

	LE Ointment N=203	Vehicle N=202	P value
Day 3	153 (75%)	95 (47%)	<0.0001
Day 8	149 (73%)	83 (41%)	<0.0001
Day 15	157 (77%)	74 (37%)	<0.0001
Day 18	132 (65%)	63 (31%)	<0.0001

There is substantial evidence of effectiveness consisting of adequate and well controlled studies which demonstrate that Lotemax (loteprednol etabonate ophthalmic ointment) 0.5% is superior to vehicle in the complete resolution of post-operative anterior chamber cell and flare and superior to vehicle in the complete resolution of post-operative pain following ocular surgery.

7. Safety

Two clinical studies (Studies 525 and 526) were used to evaluate safety in addition to the previous studies with loteprednol suspension. There were 405 patients in the safety database who received loteprednol etabonate ophthalmic ointment. In a pooled analysis of Studies 525 and 526, the most common ocular adverse events reported with loteprednol ointment 0.5% were anterior chamber inflammation, photophobia, corneal edema, conjunctival hyperemia, eye pain, and iritis.

There is substantial evidence of safety consisting of adequate and well controlled studies which demonstrate that Lotemax (loteprednol etabonate ophthalmic ointment) 0.5%, dosed four times daily beginning 24 hours after surgery and continuing throughout the first 2 weeks of the post-operative period, is safe for treatment of post-operative inflammation and pain following ocular surgery

8. Advisory Committee Meeting

No Advisory Committee Meeting was held. There were no new issues raised in the review of the application.

9. Pediatrics

Bausch & Lomb requested a pediatric waiver for Lotemax (loteprednol etabonate ophthalmic ointment) 0.5% on April 30, 2010. Safety and effectiveness in pediatric patients have not been established. Lotemax (loteprednol etabonate ophthalmic ointment) 0.5% should not be used in children following ocular surgery. Its use may interfere with amblyopia treatment by hindering the child's ability to see out of the operated eye.

10. Other Relevant Regulatory Issues

DSI

A Division of Scientific Investigations (DSI) audit was requested; DSI completed their review on September 13, 2010. Two domestic clinical sites were inspected in support of this application, Kenneth Sall, M.D. and Arthur M. Fishman, M.D.

The inspection of Dr. Sall's site revealed that the studies were not conducted in accordance with the investigational plan. A Form FDA 483, Inspectional Observations, was issued to this investigator, for: Failure to conduct the study according to the signed investigator statement and the investigational plan [21 CFR 312.60]. Specifically, three employees performed duties not delegated to them (screening visits, post surgery visit, visual acuity and refraction evaluations).

Although regulatory violations were noted as above, it is unlikely based on the nature of the violations that they significantly affect the reliability of safety and efficacy data. Based on the provided EIR for this site and Dr. Sall's responses regarding the regulatory violations during the inspection, which were documented in the EIR, data derived from Dr. Sall's site are considered reliable.

The inspection of Dr. Fishman's site did not reveal regulatory violations. Based on the provided Establishment Inspection Report (EIR) for this site, data derived from Dr. Fishman's site are considered acceptable.

FINANCIAL DISCLOSURE

The applicant has examined its financial data regarding significant payments of other sorts made to all investigators in the studies and equity information as provided by the investigators, as defined in 21 CFR 54.2. There is no evidence to suggest that the results of the study were impacted by any financial payments.

DMEPA

The Division of Medication Error Prevention and Analysis (DMEPA) Proprietary Name Risk Assessment evaluated "Lotemax" as the proposed proprietary name for loteprednol etabonate ophthalmic ointment. DMEPA approved proprietary name in a letter dated June, 4, 2010.

DDMAC

The Division of Drug Marketing, Advertising, and Communications (DDMAC) reviewed the draft product labeling, including the package insert (PI), draft carton label, and draft container label for Lotemax (loteprednol etabonate ophthalmic ointment) 0.5%. DDMAC provided recommendations on the packaging configuration and the package insert labeling in a separate review and in a labeling meeting held on September 13, 2010

11. Labeling

Lotemax (loteprednol etabonate ophthalmic ointment) 0.5% is not currently recommended for approval for the treatment of post-operative inflammation and pain following ocular surgery. Final comment on the proposed labeling for the drug product is deferred pending resolution of the outstanding manufacturing facility issues and the acceptance criterion deficiency regarding Dose Uniformity.

12. Regulatory Action

Lotemax (loteprednol etabonate ophthalmic ointment) 0.5% is not currently recommended for approval for the treatment of post-operative inflammation and pain following ocular surgery based on the outstanding cGMP issues and a lack of adequate specifications.

Manufacturing facilities for the drug substance are not in compliance with current good manufacturing practice. The current proposed acceptance criterion for Dose Uniformity is not acceptable. Satisfactory resolution of these deficiencies is required before this application may be approved.

There is substantial evidence of effectiveness consisting of adequate and well controlled studies which demonstrate that Lotemax (loteprednol etabonate ophthalmic ointment) 0.5% is superior to vehicle in the complete resolution of post-operative anterior chamber cell and flare and superior to vehicle in the complete resolution of post-operative pain following ocular surgery.

Pharmacology/Toxicology, Biostatistics, Clinical, Clinical Pharmacology, and Product Quality Microbiology have recommended approval for this application. CMC does not recommend approval based on the outstanding cGMP issues and lack of adequate specifications.

Wiley A. Chambers, MD
Acting Director
Division of Anti-Infective and Ophthalmology Products

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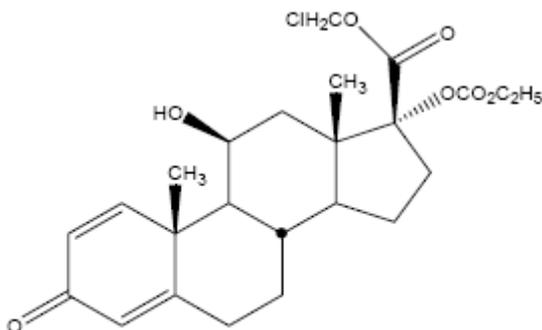
WILEY A CHAMBERS
10/20/2010

Cross-Discipline Team Leader Review for NDA 200738

Date	September 29, 2010
From	William M. Boyd, M.D.
Subject	Cross-Discipline Team Leader Review
NDA #	200738
Applicant	Bausch & Lomb Incorporated
Date of Submission	December 23, 2009
PDUFA Goal Date	October 23, 2010
Type of Application	505(b)(1)
Name	Lotemax (loteprednol etabonate ophthalmic ointment) 0.5%
Dosage forms / Strength	Topical ophthalmic ointment
Proposed Indication(s)	Treatment of post-operative inflammation and pain following ocular surgery
Recommended:	Not recommended for Approval

1. Introduction

Loteprednol etabonate ophthalmic ointment (LE) is a sterile, topical, anti-inflammatory corticosteroid formulation. The drug product, developed by B&L, is an ophthalmic ointment containing 0.5% loteprednol etabonate. The drug is (b) (4) of white petrolatum and mineral oil.



Loteprednol etabonate has been marketed in the United States by Bausch & Lomb since 1998 as Lotemax (loteprednol etabonate ophthalmic suspension) 0.5% and Alrex (loteprednol etabonate ophthalmic suspension) 0.2% and marketed since 2005 in a fixed combination with tobramycin as Zylet (loteprednol etabonate and tobramycin ophthalmic suspension).

2. Background

The product development for loteprednol etabonate ophthalmic ointment, 0.5% was conducted under IND 32,432. There was a PIND meeting on 1/24/07, EOP 2 meeting on 7/16/07, and Pre-NDA meeting on 10/7/09.

Lotemax is a topical corticosteroid. Ocular AEs generally associated with ophthalmic steroids include elevated IOP (which may be associated with optic nerve damage and visual acuity and field defects), posterior subcapsular cataract formation, secondary ocular infection from pathogens including herpes simplex, and perforation of the globe where there is thinning of the cornea or sclera. Other reactions include acute anterior uveitis, systemic hypercorticism, keratitis, conjunctivitis, corneal ulcers, mydriasis, conjunctival hyperemia, loss of accommodation, and ptosis.

3. CMC

From the CMC Review finalized 10/1/2010:

The drug substance, loteprednol etabonate, is a white to off-white powder. It is insoluble in water. The chemical name is chloromethyl 17 α -[(ethoxycarbonyl)oxy]-11 β -hydroxy-3-oxoandrosta-1,4-diene-17 β -carboxylate. The molecular formula is C₂₄H₃₁ClO₇ and the molecular weight of loteprednol etabonate is 466.96. Loteprednol etabonate is the same drug substance as is currently used in Lotemax (loteprednol etabonate ophthalmic suspension 0.5%) (NDA 20-583). The drug substance is manufactured and (b) (4) DMF (b) (4) is referenced for drug substance information.

The drug product, Lotemax (loteprednol etabonate ophthalmic ointment) 0.5%, will be manufactured at the facility in Tampa.

DESCRIPTION AND COMPOSITION OF THE DRUG PRODUCT:

The following reproduced table lists the composition of the drug product.

Table 3.2.P.1-1: Composition of Loteprednol Etabonate Ophthalmic Ointment

Component	Reference to Quality Standard	Function	Concentration (mg/g)	% w/w
Sterile Loteprednol Etabonate	In-house	Active	5.0	0.5
Mineral Oil	USP	(b) (4)		
White Petrolatum	USP	(b) (4)		

Commercial drug product will be packaged as a nominal 3.5g fill in 3.5g tin tubes with pink LDPE caps. In addition, a physician's sample size configuration consisting of a nominal 1g fill in 2g tin tubes with pink LDPE caps is also proposed. The average weight of one dose (a 1/2 inch ribbon) of ointment

was determined to be 30.0 mg with a standard deviation of 6.6 mg. Individual ½ inch ribbons ranged in weight from 16.2 mg to 48.7 mg.

FACILITY INSPECTIONS

A site recommendation of “Withhold” was made by the Office of Compliance, since manufacturing facilities for the drug substance (b) (4) are not in compliance with current good manufacturing practice.

The CMC Reviewer has not recommended approval for this application based on these outstanding cGMP issues. Satisfactory resolution of this deficiency is required before this application may be approved.

PROPOSED SPECIFICATIONS:

Drug Product Specification (Updated Sep 21, 2010)

Test	Analytical Procedure	Acceptance Criteria	
		Release	Shelf life
Description	Visual (PS-1008)	Off-white to yellowish homogeneous ointment	
Particulate Matter	Visual (PS-1013)	Essentially free of foreign particulate matter	Not applicable
Metal Particles	USP<751> (PS-1001)	(b) (4)	Not applicable
Particle Size Distribution	C-1812	(b) (4)	Not applicable
Identification A	C-1689 (HPLC)	The retention time for loteprednol etabonate peak in the sample corresponds to that of the standard	Not applicable
Identification B	C-1689 (UV)	The UV spectrum of the assay preparation exhibits its maximum at the same wavelength as that of the standard	Not applicable
Assay	C-1689 (HPLC)	(b) (4)	(b) (4)
Related Substances [^]	C-1689 (HPLC)	(b) (4)	(b) (4)

		Total Chromatographic Related Substances	NMT (b) (4)	NMT (b) (4)
(b) (4)	C-1798 (HPLC)	NMT (b) (4)		
Dose Uniformity	C-1817 (HPLC)	Not Applicable		See below*
Leak Test	USP<771> (PS-1006)	Meets USP requirements		Not applicable
Minimum Fill	USP<755> (PS-1003)	Meets USP requirements		Not applicable
(b) (4)	C-1204 (b) (4)	NMT (b) (4)		
Sterility	USP <71> 24-T012 or B-1044	Meets USP requirements		
Endotoxin	Complies with USP <85> (72-156 or STP0046)	NMT (b) (4)		Not applicable

^ Any loteprednol etabonate synthetic process impurities, which are not also shown to be degradation products, would be controlled in the drug substance in accordance with ICH Q6A.

(b) (4)

CMC finds the proposed acceptance criterion for Dose Uniformity in the above table not acceptable.

Per the original CMC review, page 96:

The proposed acceptance criteria cannot provide appropriate control on dose uniformity. It is not acceptable to establish such wide acceptance criteria for dose uniformity using samples stored at 25°C/60%RH, ranging from 3 to 32 months of age, since settling might have happened to some samples. The acceptance criteria should be established based on data from homogeneous samples (or at release) with a reasonable range considering the relative standard deviation for the analytical procedure and a risk-based assessment of the impact of settling on safety and efficacy. The dose uniformity test with appropriate acceptance criteria should be able to identify settling in samples during stability.

4. Nonclinical Pharmacology/Toxicology

From the original Pharmacology/Toxicology Review finalized 7/19/2010:

The nonclinical safety profile of loteprednol etabonate (LE) has been extensively evaluated as a 0.5% ophthalmic suspension under NDA 20-583 (approved March 1998). For the development of 0.5% loteprednol etabonate ophthalmic ointment, the sponsor has conducted 28-day ocular toxicity studies in rabbits and dogs. The study reports showed no significant toxicity findings except for the transient irregular aspect of ocular surface (in both treated and control groups) caused by the viscous consistency of the ointment vehicle.

The formulation of 0.5% loteprednol etabonate ophthalmic ointment contains (b) (4) mineral oil (USP) and (b) (4) petrolatum (USP) (b) (4). Many of the FDA approved ophthalmic drug products contain up to 59.5% mineral oil and up to 85% petrolatum.

The current label for the marketed loteprednol etabonate (LE) states that LE was not genotoxic in a battery of genotoxicity tests. LE has been shown to be embryotoxic and teratogenic. No carcinogenic studies have been conducted for LE.

5. Clinical Pharmacology/Biopharmaceutics

From the original Clinical Pharmacology Review finalized 8/20/2010:

The current original NDA 505(b)(1) application presents data from two adequate and well-controlled superiority studies of loteprednol etabonate ointment compared to vehicle for replicative evidence of safety and efficacy of the ointment formulation. A single dose level of loteprednol etabonate ointment was studied in these Phase 3 trials and no assessments of exposure were obtained, thus an exposure-response analysis could not be conducted. Clinical pharmacokinetic studies were conducted during the development of Lotemax suspension and Zylet, and these data have been submitted previously with the corresponding NDAs for these products (NDA #20-583 and #50-804, respectively). No new clinical pharmacology data was presented in this application.

The pharmacokinetic data previously submitted addresses requirement for bioavailability outlined in 21 CFR 320.21.

6. Sterility Assurance

From the original Product Quality Microbiology Review finalized 7/2/2010:

(b) (4)

The drug product is a sterile topical ophthalmic ointment in a multi-dose tube. A microbial ingress test was used to validate container closure integrity for the tin tubes. The study was performed using 3.5 g tubes with LDPE caps. Media-filled tubes were immersed in a suspension of *B. cepacia* (6.2×10^8 CFU/mL) for 20 minutes at room temperature. Following immersion, the test samples were subjected to 5 psi (above atmospheric) of pressure for 5 minutes followed by 5 minutes at 5 inches of mercury (vacuum). The test units were then incubated at $32.5 \pm 2.5^\circ\text{C}$ for 7 days. After incubation, the contents of the test units were examined for evidence of microbial growth. None of the test units or negative controls (not immersed in the microbial suspension) was positive for growth. The growth promotion

units (inoculated with 10-100 CFU of *B. cepacia*) and the positive control units (breached units) were positive for microbial growth.

(b) (4)
 The drug product was tested using USP <51> antimicrobial effectiveness testing. In addition to the 5 test organisms listed in USP <51>, four additional organisms were used in the test. The acceptance criteria were achieved for a USP Category 1 product (includes ophthalmic products).

7. Clinical/Statistical - Efficacy

From the original Medical Officer Review dated 9/27/2010:

Analyses of Primary Endpoints

The hierarchical primary efficacy endpoints for these two phase 3 studies were:

1. The proportion of subjects with complete resolution of anterior chamber cells and flare at Visit 5 (POD# 8)
2. The proportion of subjects with Grade 0 (no pain) at Visit 5 (POD# 8).

Study 525: Primary Efficacy Analysis (ITT Population)

	LE Ointment N=201	Vehicle N=199	P value
Complete resolution of AC cells and flare at Visit 5 (POD #8)			
Yes	48 (23.9%)	27 (13.6%)	0.0022
No	153 (76.1%)	172 (86.4%)	
Subjects without Rescue Medication	139	109	
Subjects with Rescue Medication	12	59	
Subjects with Missing Data	2	4	
Complete resolution of pain at Visit 5 (POD #8)			
Yes	156 (77.6%)	90 (45.2%)	<0.0001
No	45 (22.4%)	109 (54.8%)	
Subjects without Rescue Medication	31	46	
Subjects with Rescue Medication	12	59	
Subjects with Missing Data	2	4	

Study 525: Primary Efficacy Analysis (PP Population)

	LE Ointment N=171	Vehicle N=170	P value
Complete resolution of AC cells and flare at Visit 5			

(POD #8)			
Yes	42 (24.6%)	22 (12.9%)	0.0009
No	129 (75.4%)	148 (87.1%)	
Subjects without Rescue Medication	121	98	
Subjects with Rescue Medication	8	50	
Subjects with Missing Data	0	0	
Complete resolution of pain at Visit 5 (POD #8)			
Yes	133 (77.8%)	79 (46.5%)	<0.0001
No	38 (22.2%)	91 (53.5%)	
Subjects without Rescue Medication	30	41	
Subjects with Rescue Medication	8	50	
Subjects with Missing Data	0	0	

Study 526: Primary Efficacy Analysis (ITT Population)

	LE Ointment N=203	Vehicle N=202	P value
Complete resolution of AC cells and flare at Visit 5 (POD #8)			
Yes	64 (31.5%)	23 (11.4%)	0.0001
No	139 (68.5%)	179 (88.6%)	
Subjects without Rescue Medication	114	108	
Subjects with Rescue Medication	23	70	
Subjects with Missing Data	2	1	
Complete resolution of pain at Visit 5 (POD #8)			
Yes	149 (73.4%)	83 (41.1%)	<0.0001
No	54 (26.6%)	119 (58.9%)	
Subjects without Rescue Medication	29	48	
Subjects with Rescue Medication	23	70	
Subjects with Missing Data	2	1	

Study 526: Primary Efficacy Analysis (PP Population)

	LE Ointment N=180	Vehicle N=173	P value
Complete resolution of AC cells and flare at Visit 5 (POD #8)			
Yes	58 (32.2%)	19 (11.0%)	<0.0001
No	122 (67.8%)	154 (89.0%)	
Subjects without Rescue Medication	103	95	
Subjects with Rescue Medication	19	59	
Subjects with Missing Data	0	0	
Complete resolution of pain at Visit 5 (POD #8)			
Yes	133 (73.9%)	71 (41.0%)	<0.0001
No	47 (26.1%)	102 (59.0%)	
Subjects without Rescue Medication	28	43	
Subjects with Rescue Medication	19	59	

Subjects with Missing Data	0	0	
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The primary efficacy analysis of the two phase 3 studies was based on the Intent to Treat (ITT) study population, which included all subjects under the treatment to which they were randomized.

Loteprednol etabonate ophthalmic ointment was superior to vehicle in the complete resolution of anterior chamber cell and flare at Visit 5 and superior to vehicle in the complete resolution of pain at Visit 5 in Studies 525 and 526. The results of the PP analysis are similar to the ITT analysis.

Efficacy Summary Statement

There is substantial evidence of effectiveness consisting of adequate and well controlled studies which demonstrate that Lotemax (loteprednol etabonate ophthalmic ointment) 0.5% is superior to vehicle in the complete resolution of post-operative anterior chamber cell and flare and superior to vehicle in the complete resolution of post-operative pain following ocular surgery.

8. Safety

From the original Medical Officer Review dated 9/27/2010:

Two clinical studies (Studies 525 and 526) were used to evaluate safety. Between the 2 studies there were 405 patients in the safety database who received loteprednol etabonate ophthalmic ointment.

Overall Exposure at Appropriate Doses/Durations

Study 525: Treatment Exposure (Safety Population)

	LE Ointment N=201	Vehicle N=199
Days of Exposure		
Mean (sd)	13.2 (3.06)	9.2 (5.10)
Minimum	2	1
Maximum	20	20

Study 526: Treatment Exposure (Safety Population)

	LE Ointment N=204	Vehicle N=201
Days of Exposure		
Mean (sd)	12.7 (3.75)	8.8 (5.15)
Minimum	1	1
Maximum	19	19

Only one dosing regimen was studied, Lotemax ointment 0.5% QID.

Long-term safety and effectiveness were not evaluated for the clinical studies. The duration of treatment for the subjects in these trials was no longer than 14 days. Loteprednol etabonate ophthalmic ointment is intended for short-term use for the treatment of inflammation and pain following ocular surgery.

Subject Disposition

Study 525: Patient Disposition

	LE Ointment	Vehicle
Total Number of Subjects Randomized	201	199
Safety Population	201	199
ITT Population	201	199
PP Population	171	170
Reason For Discontinuation		
Withdrawal by subject	0	4
AE	0	1
Investigator Decision	0	1
Failure to follow study protocol	1	0

Study 526: Patient Disposition

	LE Ointment	Vehicle
Total Number of Subjects Randomized	203	202
Safety Population	204	201
ITT Population	203	202
PP Population	180	173
Reason For Discontinuation		
Lost to f/u	1	0
AE	0	2
Travel problem	1	0
Failure to follow study protocol	1	0

Study 525: Primary Reason for Subject Discontinuation

	LE Ointment N=201	Vehicle N=199
Withdrawal by subject	0	4
AE	0	1 *
Investigator decision	0	1
Failure to follow study procedures	1	0

*At site #461665, subject ID #0335, a 79-year-old white female, who enrolled in the study on 1/14/09, discontinued on 1/23/09 due to an SAE (severe endophthalmitis). See section 7.3.2 for more details.

Study 526: Primary Reason for Subject Discontinuation

	LE Ointment N=203	Vehicle N=202
Lost to f/u	1	0
AE	0	2 *
Failure to follow study procedures	1	0
Travel problem	1	0

*At site #987168, subject ID #1213, an 80 yo female subject, who began to receive treatment on 10/31/08, had an SAE (severe fall of unknown cause and broken hip). This subject discontinued the study on 11/11/08 due to the SAE. At site #990165, subject ID #1232, a 66 yo white male, whose screening visit was 10/28/08, discontinued due to an SAE (worsening diabetic foot ulcer) and discontinued on 11/19/08.

Adverse Events

Table 2: Ocular TEAEs in $\geq 3\%$ Study Eyes, Either Treatment Group, Prior to Rescue Medication Use, Integrated Analyses - Safety Population

	LE Ointment (N = 405)	Vehicle (N = 400)	p-Value ¹
Total Number of AEs	313	581	
Number of Subjects with at Least 1 AE	191 (47.2%)	312 (78.0%)	< 0.0001
SYSTEM ORGAN CLASS (SOC) Preferred Term (PT)			
EYE DISORDERS	189 (46.7%)	312 (78.0%)	< 0.0001
Anterior chamber inflammation	110 (27.2%)	200 (50.0%)	< 0.0001
Eye pain	15 (3.7%)	43 (10.8%)	0.0001
Photophobia	22 (5.4%)	31 (7.8%)	0.2025
Conjunctival hyperaemia	16 (4.0%)	30 (7.5%)	0.0336
Iritis	15 (3.7%)	31 (7.8%)	0.0149
Corneal oedema	18 (4.4%)	23 (5.8%)	0.4264
Ciliary hyperaemia	10 (2.5%)	23 (5.8%)	0.0208
Lacrimation increased	8 (2.0%)	19 (4.8%)	0.0318
Anterior chamber cell	10 (2.5%)	16 (4.0%)	0.2375
Eye pruritus	6 (1.5%)	19 (4.8%)	0.0080
Anterior chamber flare	6 (1.5%)	14 (3.5%)	0.0731

¹p-Value based on Fisher's Exact test.

Note: A subject was counted at most once for a given preferred term (except for total number of AEs).

Source: 2.7.4.7 Appendix A, Table 3.7.5.1

Source - Page 11, ISS

In a pooled analysis of Studies 525 and 526, the most common ocular adverse events reported with loteprednol ointment 0.5% were anterior chamber inflammation, photophobia, corneal edema, conjunctival hyperemia, eye pain, and iritis.

Corticosteroids have a known risk of increasing IOP, and therefore IOP was monitored at every visit.

Study 525: Highest IOP at Any Visit (Safety Population)

	LE Ointment N=201	Vehicle N=197
Mean (sd)	15.9 (3.15)	14.3 (3.41)
<=5	0	1
6-14	58	99
15-21	139	94
22-29	3	3
>=30	1	0
Change From Baseline Worst Visit (Highest IOP)		
Mean (sd)	0.0 (3.02)	-1.8 (4.72)
<=-15	0	3
-14 to -10	1	6
-9 to -5	11	37
-4 to 0	106	90
1 to 4	68	48
5 to 9	15	12
10 to 14	0	1
15 to 19	0	0
>=20	0	0

Study 526: Highest IOP at Any Visit (Safety Population)

	LE Ointment N=203	Vehicle N=199
Mean (sd)	15.9 (2.77)	14.9 (3.12)
<=5	0	0
6-14	63	84
15-21	136	112
22-29	4	3
>=30	0	0
Change From Baseline Worst Visit (Highest IOP)		
Mean (sd)	0.1 (3.34)	-0.9 (4.24)
<=-15	0	1
-14 to -10	0	4
-9 to -5	19	26
-4 to 0	95	99
1 to 4	72	48
5 to 9	14	21
10 to 14	3	0
15 to 19	0	0
>=20	0	0

Deaths

There were no deaths in either Study 525 or 526.

Safety Summary Statement

There is substantial evidence of safety consisting of adequate and well controlled studies which demonstrate that Lotemax (loteprednol etabonate ophthalmic ointment) 0.5%, dosed four times daily beginning 24 hours after surgery and continuing throughout the first 2 weeks of the post-operative period, is safe for treatment of post-operative inflammation and pain following ocular surgery

In a pooled analysis of Studies 525 and 526, the most common ocular adverse events reported with loteprednol ointment 0.5% were anterior chamber inflammation, photophobia, corneal edema, conjunctival hyperemia, eye pain, and iritis.

9. Advisory Committee Meeting

No Advisory Committee Meeting was held. There were no new issues raised in the review of the application which were thought to benefit from an Advisory Committee Meeting.

10. Pediatrics

Bausch & Lomb requested a pediatric waiver for Lotemax (loteprednol etabonate ophthalmic ointment) 0.5% on April 30, 2010.

Safety and effectiveness in pediatric patients have not been established.

Lotemax (loteprednol etabonate ophthalmic ointment) 0.5% should not be used in children following ocular surgery. Its use may interfere with amblyopia treatment by hindering the child's ability to see out of the operated eye.

11. Other Relevant Regulatory Issues

DSI

A Division of Scientific Investigations (DSI) audit was requested; DSI completed their review on September 13, 2010. Two domestic clinical sites were inspected in support of this application, Kenneth Sall, M.D. and Arthur M. Fishman, M.D.

Per the DSI Summary:

The inspection of Dr. Sall's site revealed that the studies were not conducted in accordance with the investigational plan. A Form FDA 483, Inspectional Observations, was issued to this investigator, for: Failure to conduct the study according to the signed investigator statement and the investigational plan [21 CFR 312.60]. Specifically, three employees performed duties not delegated to them (screening visits, post surgery visit, visual acuity and refraction evaluations).

Although regulatory violations were noted as above, it is unlikely based on the nature of the violations that they significantly affect the reliability of safety and efficacy data. Based on the provided EIR for this site and Dr. Sall's responses regarding the regulatory violations during the inspection, which were documented in the EIR, data derived from Dr. Sall's site are considered reliable.

The inspection of Dr. Fishman's site did not reveal regulatory violations. Based on the provided Establishment Inspection Report (EIR) for this site, data derived from Dr. Fishman's site are considered acceptable.

FINANCIAL DISCLOSURE

The applicant has examined its financial data regarding significant payments of other sorts made to all investigators in the studies and equity information as provided by the investigators, as defined in 21 CFR 54.2. There is no evidence to suggest that the results of the study were impacted by any financial payments.

DMEPA

The Division of Medication Error Prevention and Analysis (DMEPA) Proprietary Name Risk Assessment evaluated "Lotemax" as the proposed proprietary name for loteprednol etabonate ophthalmic ointment. DMEPA approved proprietary name in a letter dated June, 4, 2010.

DMEPA provided recommendations on the packaging configuration and the package insert labeling in a separate review and in a labeling meeting held on September 13, 2010.

DDMAC

The Division of Drug Marketing, Advertising, and Communications (DDMAC) reviewed the draft product labeling, including the package insert (PI), draft carton label, and draft container label for Lotemax (loteprednol etabonate ophthalmic ointment) 0.5%. DDMAC provided recommendations on the packaging configuration and the package insert labeling in a separate review and in a labeling meeting held on September 13, 2010.

BIOSTATISTICS

Per the Biostatistics consultative review finalized 8/19/2010:

After the NDA submission, the Agency identified that one of the investigators of study 525, Dr. Kenneth (Sall Research Medical Center), could be problematic. The Agency requested the applicant to remove all data from the Sall Research Medical Center (Dr. Kenneth Sall) investigator site. Re-analyses of the efficacy dataset, after removing this problematic site, showed the efficacy results were consistent with the primary analyses.

In studies 525 and 526, both tests of primary efficacy endpoints proved successful in the ITT population at Visit 5 (Day 8), while considering subjects with missing values and subjects requiring rescue medication as treatment failures:

- LE Ophthalmic Ointment, 0.5% was superior to Vehicle and efficacious in resolution of anterior chamber cells and flare at Postoperative Day 8.
- LE Ophthalmic Ointment, 0.5% was also superior to Vehicle and efficacious in the treatment of pain following cataract surgery at Postoperative Day 8.

Pharmacology/Toxicology, Clinical Pharmacology, Product Quality Microbiology, Clinical, and Biostatistics recommend approval of this new drug application. CMC does not recommend approval based on the outstanding cGMP inspections issues and the unacceptable acceptance criterion for Dose Uniformity.

12. Labeling

Lotemax (loteprednol etabonate ophthalmic ointment) 0.5% is not currently recommended for approval for the treatment of post-operative inflammation and pain following ocular surgery based on the outstanding cGMP issues.

Final comment on the proposed labeling for the drug product is deferred pending resolution of the outstanding manufacturing facility issues and the acceptance criterion deficiency regarding Dose Uniformity.

13. Recommendations/Risk Benefit Assessment

RECOMMENDED REGULATORY ACTION:

Lotemax (loteprednol etabonate ophthalmic ointment) 0.5% is not currently recommended for approval for the treatment of post-operative inflammation and pain following ocular surgery based on the outstanding cGMP issues.

Manufacturing facilities for the drug substance are not in compliance with current good manufacturing practice. The current proposed acceptance criterion for Dose Uniformity is not acceptable. Satisfactory resolution of these deficiencies is required before this application may be approved.

RISK BENEFIT ASSESSMENT:

There is substantial evidence of effectiveness consisting of adequate and well controlled studies which demonstrate that Lotemax (loteprednol etabonate ophthalmic ointment) 0.5% is superior to vehicle in the complete resolution of post-operative anterior chamber cell and flare and superior to vehicle in the complete resolution of post-operative pain following ocular surgery.

When looking at the Intent-to-Treat (ITT) population for complete resolution of AC cell/flare and pain, loteprednol etabonate ophthalmic ointment, 0.5% is superior to vehicle in Studies 525 and 526. The results of the Per-Protocol PP analysis are similar to the ITT analysis.

In a pooled analysis of Studies 525 and 526, the most common ocular adverse events reported with loteprednol ointment 0.5% were anterior chamber inflammation, photophobia, corneal edema, conjunctival hyperemia, eye pain, and iritis.

The benefits of using this drug product outweigh the risks for the above indication.

Pharmacology/Toxicology, Biostatistics, Clinical, Clinical Pharmacology, and Product Quality Microbiology have recommended approval for this application. CMC does not recommend approval based on the outstanding cGMP issues and the acceptance criterion deficiency regarding Dose Uniformity.

RECOMMENDATION FOR POSTMARKETING RISK MANAGEMENT ACTIVITIES:

There are no risk management activities recommended beyond the routine monitoring and reporting of all adverse events.

There are no recommended Postmarketing Requirements or Phase 4 Commitments.

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/s/

WILLIAM M BOYD
10/13/2010

WILEY A CHAMBERS
10/20/2010

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	200738
Letter Date	12/22/09
Stamp Date	12/23/09
PDUFA Goal Date	10/23/10
Reviewer Name	Sonal D. Wadhwa, MD
Review Completion Date	8/9/10
Established Name	Loteprednol etabonate ophthalmic ointment, 0.5%
(Proposed) Trade Name	Lotemax
Therapeutic Class	Corticosteroid
Applicant	Bausch and Lomb
Priority Designation	S
Formulation	Ointment
Dosing Regimen	QID x 14 days
Indication	Treatment of post-operative inflammation and pain following ocular surgery
Intended Population	Patients s/p ocular surgery with inflammation

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

NDA 200-738 is recommended for approval with the revised labeling identified in this review. The clinical studies contained in this submission support the use of loteprednol etabonate ophthalmic ointment, 0.5% for the treatment of inflammation and pain following ocular surgery.

1.2 Risk Benefit Assessment

The benefits of using this drug product outweigh the risks for the above indication.

1.3 Recommendations for Postmarketing Risk Management Activities

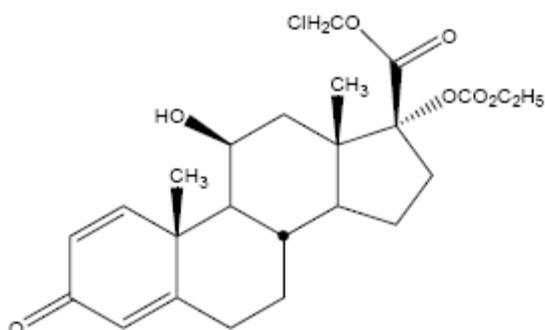
There are no proposed risk management actions except the usual post-marketing collection and reporting of adverse experiences associated with the use of drug product.

1.4 Recommendations for other Post Marketing Study Commitments

There are no recommended Phase 4 clinical study commitments.

2 Introduction and Regulatory Background

2.1 Product Information



The loteprednol etabonate ophthalmic ointment (LE) is a sterile, topical, anti-inflammatory corticosteroid formulation. The drug product, developed by B&L, is an ophthalmic ointment

containing 0.5% loteprednol etabonate. The drug is (b) (4) of white petrolatum and mineral oil.

2.2 Tables of Currently Available Treatments for Proposed Indications

Name of Drug	Indication
Xibrom	Treatment of post-operative inflammation and reduction of ocular pain in patients who have undergone cataract extraction.
Voltaren	Treatment of post-operative inflammation in patients who have undergone cataract extraction and for the temporary relief of pain and photophobia in patients undergoing corneal refractive surgery.
Acular LS	Reduction of ocular pain and burning/stinging following corneal refractive surgery.
Acular	Temporary relief of ocular itching due to seasonal allergic conjunctivitis. Acular is also indicated for the treatment of post-operative inflammation in patients who have undergone cataract extraction.
Nevanac	Treatment of pain and inflammation associated with cataract surgery.
Vexol	Treatment of post-operative inflammation following ocular surgery and in the treatment of anterior uveitis.
Durezol	Treatment of inflammation and pain following ocular surgery.

2.3 Availability of Proposed Active Ingredient in the United States

Loteprednol etabonate has been marketed in the US since 1998 as Lotemax and Alrex ophthalmic suspension drug products and since 2005 in a fixed combination with tobramycin as Zylet.

Drug	NDA	Indication
Lotemax (loteprednol etabonate ophthalmic suspension, 0.5%)	20-583	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, SPK, herpes zoster keratitis, iritis, cyclitis, selected infective conjunctivides, when the inherent hazard of steroid use is accepted to obtain an advisable diminution in edema and inflammation. It is also indicated for the treatment of post-operative inflammation following ocular surgery.
Alrex (loteprednol etabonate ophthalmic suspension, 0.2%)	20-803	Temporary relief of the signs and symptoms of seasonal allergic conjunctivitis.
Zylet (loteprednol etabonate 0.5% and tobramycin 0.3% ophthalmic suspension)	50-804	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.

2.4 Important Safety Issues With Consideration to Related Drugs

Lotemax is a topical corticosteroid. Ocular AEs generally associated with ophthalmic steroids include elevated IOP (which may be associated with optic nerve damage and visual acuity and field defects), posterior subcapsular cataract formation, secondary ocular infection from pathogens including herpes simplex, and perforation of the globe where there is thinning of the cornea or sclera. Other reactions include acute anterior uveitis, systemic hypercorticoidism, keratitis, conjunctivitis, corneal ulcers, mydriasis, conjunctival hyperemia, loss of accommodation, and ptosis.

2.5 Summary of Pre-submission Regulatory Activity Related to Submission

The product development for loteprednol etabonate ophthalmic ointment, 0.5% was conducted under IND 32,432. There was a PIND meeting on 1/24/07, EOP 2 meeting on 7/16/07, and Pre-NDA meeting on 10/7/09.

2.6 Other Relevant Background Information

None.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

DSI was consulted for this study. DSI inspected 2 sites: Dr. Sall and Dr. Fishman. Dr. Sall was chosen because a former employees' misconduct may have affected his data in other trials. Both inspections revealed no problems with the data for these trials.

3.2 Compliance with Good Clinical Practices

There is no evidence to suggest that the clinical trials were not conducted in compliance with good clinical practices.

3.3 Financial Disclosures

Financial disclosure forms for Studies 525 and 526 were reviewed. There were no investigators with proprietary interest or with any significant interest in the drug product. (b) (6) (b) (6) did reveal he receives \$70,000 annually from Bausch and Lomb in consulting fees; however, this is unlikely to affect the results of the trial. (b) (6) also did reveal he is a medical consultant for Bausch and Lomb and receives compensation on a per project basis; however, this too is unlikely to affect the results of the trial.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Qualitative and quantitative composition of Loteprednol Etabonate Ophthalmic Ointment

Component	Reference to Quality Standard	Function	Concentration (mg/g)	% w/w
Sterile Loteprednol Etabonate	In-house	Active	5.0	0.5
Mineral Oil	USP	(b) (4)	(b) (4)	(b) (4)
White Petrolatum	USP			

4.2 Clinical Microbiology

There is no clinical microbiology review for this product. It is not an anti-infective.

4.3 Preclinical Pharmacology/Toxicology

Non-clinical ocular toxicity studies with 0.5% loteprednol etabonate ophthalmic suspension have been conducted in rabbits for up to 26-week and in dogs for up to 52- week in NDA 20-583. For the development of 0.5% loteprednol etabonate ophthalmic ointment, the sponsor has conducted a single dose pharmacokinetic study in pigmented rabbits and 28 day repeat dose study in rabbits and dogs. The study reports showed no significant toxicity findings except for the irregular aspect of ocular surface caused by the viscous consistency of the ointment vehicle.

The formulation of 0.5% loteprednol etabonate ophthalmic ointment contains (b) (4) mineral oil and (b) (4) petrolatum as the ointment bases. Many of the FDA approved ophthalmic drug products contain up to 59.5% mineral oil and up to 85% petrolatum. The current label for the marketed loteprednol etabonate stated that LE was not genotoxic in a battery of genotoxicity tests. LE has been shown to be embryotoxic and teratogenic. No carcinogenic studies have been conducted for LE.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Lotemax ointment is topical, anti-inflammatory corticosteroid.

4.4.2 Pharmacodynamics

Not performed for this application.

4.4.3 Pharmacokinetics

Clinical pharmacokinetic studies were conducted during the development of Lotemax (Loteprednol Etabonate Ophthalmic Suspension, 0.5%) and Zylet (Loteprednol Etabonate 0.5% and Tobramycin 0.3% Ophthalmic Suspension), and the data has been submitted previously in the NDAs for these products.

Results from a bioavailability study with Lotemax suspension in normal volunteers established that plasma levels of LE and 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 1 drop in each eye of LE suspension 0.5%, 8 times daily for 2 days and then 4 times daily (QID) for 41 days. Because the ointment formulation of LE is not expected to produce higher systemic exposure than the suspension formulation of LE, there were no clinical PK studies conducted with the ointment formulation.

5 Sources of Clinical Data

5.1 Tables of Clinical Studies

Type of Study	Study Identifier	Study Design	Study Objective	Test Product	Number of Subjects	Type of Subjects
Safety and efficacy	525	Multi-center, randomized, double-masked, parallel, vehicle controlled	Evaluate the safety and efficacy of LE ointment vs. vehicle in the treatment of post-operative inflammation and pain	LE ointment 0.5% or vehicle QID for 14 days	400	Clinical diagnosis of post-operative inflammation (ACR \geq 3)
Safety and efficacy	526	Multi-center, randomized, double-masked, parallel, vehicle controlled	Evaluate the safety and efficacy of LE ointment vs. vehicle in the treatment of post-operative inflammation and pain	LE ointment 0.5% or vehicle QID for 14 days	405	Clinical diagnosis of post-operative inflammation (ACR \geq 3)

5.2 Review Strategy

The sources of clinical data utilized in this review include the studies listed in section 5.1.

5.3 Discussion of Individual Studies

STUDIES 525 and 526

These studies were randomized, multicenter, double-masked, parallel-group, vehicle-controlled studies to evaluate the clinical safety and efficacy of LE ophthalmic ointment, 0.5% compared to vehicle for the treatment of inflammation following cataract surgery. Subjects were randomized, in a 1:1 ratio stratified by site, to receive either test or control. Study duration was approximately four weeks, and each subject was expected to visit the clinic seven times. Visit 1 (Screening Visit) occurred in the 14 days prior to surgery. Visit 2 was the day of surgery. At Visit 3 (POD# 1) eligibility was assessed and if eligible, the subject was assigned to one of the two randomized treatment groups. During the study, each subject self-administered approximately a one-half inch long ribbon of study drug to the lower cul-de-sac of the study eye QID at approximately four hour intervals. The initial dose occurred in the clinic, at Visit 3 (POD# 1). Study treatment lasted approximately 14 days with the last administration being the fourth dose on the day before Visit 6. Assessments at each visit included ocular signs and symptoms, visual acuity, funduscopy, IOP, and adverse events.

Inclusion Criteria

- Subjects ≥ 18 years of age
- Subjects who had the ability to understand and sign an ICF and provided HIPAA authorization
- Subjects who were a candidate for routine, uncomplicated cataract surgery (phacoemulsification with PCIOL, not combined with any other surgery)
- Subjects who, in the Investigator's opinion, had potential post-operative pin-holed Snellen VA of at least 20/200 in the study eye
- Subjects who were not of childbearing potential or subjects who had a negative urine pregnancy test result at screening
- Subjects must have been able and willing to comply with all treatment and follow-up procedures
- In addition, this study included subjects who met the following inclusion criteria at Visit 3 (POD# 1):
 - Subjects who had undergone routine, uncomplicated cataract surgery (phacoemulsification with PCIOL, not combined with any other surgery)
 - Subjects who had an ACR combined grade of at least 3 at POD# 1

Exclusion Criteria

- Subjects who were expected to require concurrent ocular therapy (either eye) NSAIDs, mast cell stabilizers, antihistamines, or decongestants during the 18 days following cataract surgery or had used any of the above within two days prior to surgery (intraoperative NSAIDs for mydriasis were permitted)
- Subjects who were expected to require treatment with systemic or ocular (either eye) corticosteroids during the 18 days following cataract surgery or had used any systemic or ocular corticosteroids within 14 days prior to cataract surgery

- Subjects who were expected to require concurrent ocular therapy with immunosuppressants (ie. Restasis) during the 18 days following cataract surgery or had used ocular immunosuppressants within 30 days prior to surgery
- Subjects who had known hypersensitivity or contraindication to the study drug or their components
- Subjects who had a history or presence of chronic generalized systemic disease that the Investigator felt might increase the risk to the subject or confound the result of the study
- Subjects who had a severe/serious ocular condition, or any other unstable medical condition that, in the Investigator's opinion, may have precluded study treatment or follow-up
- Subjects with IOP \geq 21 mm Hg, uncontrolled glaucoma, or treated for glaucoma in the study eye
- Subjects who were monocular or had pin-holed Snellen VA 20/200 or worse in the non-study eye
- Subjects who had ocular surgery (including laser surgery) in the study eye within 3 months or in the fellow eye within 2 weeks prior to the Screening Visit
- Subjects who were sexually active and who did not fall into one of the following categories:
 - Postmenopausal
 - Surgically sterile
 - Used one of the following birth control methods throughout the duration of the study:
 - Intrauterine device (> 14 days)
 - Barrier method (condom or diaphragm) with spermicide (> 14 days)
 - Hormonal contraception (same dose and same formulation for at least six months)
- Women who were pregnant or breastfeeding
- Subjects who had participated in an investigational drug or device study within the last 30 days prior to the Screening Visit
- Subjects who were previously randomized in this study

Grading Scales Used for the Studies

Anterior Chamber Cell Grading

- 0 = No cells seen
- 1 = 1 - 5 cells
- 2 = 6 - 15 cells
- 3 = 16 - 30 cells
- 4 = >30 cells

Anterior Chamber Flare Grading

- | | |
|-----------------|--|
| 0 = None | No Tyndall effect |
| 1 = Mild | Tyndall effect barely discernible |
| 2 = Moderate | Tyndall effect in anterior chamber is moderately intense. Iris pattern is seen clearly |
| 3 = Severe | Tyndall effect in AC is severely intense. Iris pattern cannot be seen clearly |
| 4 = Very severe | Tyndall effect is very severely intense. The aqueous has a white and milky appearance |

Ocular Pain Grading: Ocular pain defined as a positive sensation of the eye, including FBS, stabbing, throbbing, or aching.

- | | |
|-----------------|---|
| 0 = None | Absence of positive sensation |
| 1 = Minimal | Presence of mild sensation or discomfort typical of post-operative ocular surgery (ie. diffuse or focal foreign body sensation, mild transient burning or stinging, etc.) |
| 2 = Mild | Mild, tolerable aching of the eye |
| 3 = Moderate | Moderate or more prolonged aching sufficient to require the use of OTC analgesics (ie. acetaminophen) |
| 4 = Mod. Severe | More prolonged aching requiring the use of an OTC analgesic other than acetaminophen |
| 5 = Severe | Intense ocular, periocular or radiating pain (ie. constant or nearly constant sharp stabbing pain, throbbing or aching, etc.) requiring prescription analgesics |

The sum of anterior chamber cell and flare scores was defined as Anterior Chamber Reaction (ACR) in the study protocol.

Clinical Review
 Sonal D. Wadhwa, MD
 NDA 200-738
 Lotemax (loteprednol etabonate ophthalmic ointment) 0.5%

Study 525: Table of Investigators

Principal Investigator	Number of Patients Enrolled
David Brown, MD Ft. Myers, FL	9
Raymond DeBarge, MD Ft. Oglethrope, GA	32
William Flynn, MD, OD San Antonio, TX	21
Jospeh P. Gira, MD Des Peres, MO	34
Michael Graham, MD Orlando, FL	47
Paul Hartman, MD Rochester, NY	23
John Hunkeler, MD Overland Park, KS	18
Kashyap Kansupada, MD Belmont, NC	16
Michael Korenfeld, MD Washington, MO	43
Stephen Lane, MD Stillwater, MN	8
Thomas Macejko, MD Fairfield, OH	9
Jonathan I. Macy, MD Los Angeles, CA	0
James McDonald, II, MD Fayetteville, AK	0
James Peace, MD Inglewood, CA	17
Timothy Peters, MD Portsmouth, NH	48
Michael Rotberg, MD Charlotte, NC	9
Kenneth Sall, MD Artesia, CA	36
Stefan Trocme, MD Cleveland, OH	11
Farrell C. Tyson, II, MD Cape Coral, FL	19
Stephen A. Updegraff, MD St. Petersburg, FL	0
TOTAL	400

Clinical Review
 Sonal D. Wadhwa, MD
 NDA 200-738
 Lotemax (loteprednol etabonate ophthalmic ointment) 0.5%

Study 526: Table of Investigators

Principal Investigator	Number of Patients Enrolled
Robert Arleo, MD Ithaca, NY	0
Patrick Arnold, MD Fort Collins, CO	16
Ralph Chu, MD Bloomington, MN	0
Lisa Cibik, MD Monroeville, PA	0
Andrew J. Cottingham, MD San Antonio, TX	21
Thomas Croley, MD Ocala, FL	23
Arthur M. Fishman, MD Pembroke Pines, FL	47
Walter Fried, MD Gurnee, IL	24
Gregory L. Henderson, MD Brandon, FL	9
Douglas Lorenz, MD Henderson, NV	40
Satish S. Modi, MD Poughkeepsie, NY	20
Bernard R. Perez, MD Tampa, FL	38
Harvey Reiser, MD Kingston, PA	33
Stephen Smith, MD Ft. Meyers, FL	44
Robert Smyth-Medina, MD Mission Hills, CA	2
William Colby Stewart, MD Houston, TX	10
Lloyd R. Taustine, MD Louisville, KY	27
Michael Tepedino, MD High Point, NC	39
Thomas Walters, MD Austin, TX	12
TOTAL	405

Study Schedule

PROCEDURE/ASSESSMENTS ¹	Visit 1 Screening	Visit 2 Surgery ²	Visit 3 Postoperative Day 1 ⁴	Visit 4 Postoperative Day 3 (± 1 Day)	Visit 5 Postoperative Day 8 (± 1 Day)	Visit 6 Postoperative Day 15 (± 1 Day)	Visit 7 Postoperative Day 18 (± 1 Day)
Informed Consent and HIPAA	X						
Urine Pregnancy Test, as applicable	X						
Demographics	X						
Current and Relevant Medical/Ophthalmic History	X						
Ocular Symptoms	X		X	X	X	X	X
Pin-holed Snellen VA	X		X	X	X	X	X
Slit Lamp Biomicroscopy	X		X	X	X	X	X
Funduscopy	X					X	
IOP (Goldman applanation tonometry or equivalent)	X		X	X	X	X	X
Determine eligibility	X		X				
AEs ³ and Concomitant Medications	X	X	X	X	X	X	X
Weigh Study Drug			X	X	X	X	
Dispense Study Drug and Diaries			X ⁵	X ⁶	X ⁶		
Collect Study Drug and Diaries				X ⁶	X ⁶	X	
Exit Study							X

¹ All ophthalmic assessments were performed bilaterally.

² Visit 2 occurred within 14 days of Visit 1. Screening and surgery could not take place on the same day.

³ Collection of AEs extended from the time the subject gave informed consent until the last study visit.

⁴ Visit 3 (Postoperative Day 1/Randomization) occurred 18 to 34 hours post-surgery. During this visit subject eligibility was confirmed based on the ACR.

⁵ Subjects instilled initial dose while in clinic.

6 Review of Efficacy

Efficacy Summary

6.1 Indication

The proposed indication: Treatment of post-operative inflammation and pain following ocular surgery.

6.1.1 Methods

The support for efficacy is from 2 clinical studies (Studies 525 and 526).

6.1.2 Demographics

Study 525: Subject Demographics (ITT Population)

Parameter	LE Ointment N=201	Vehicle N=199
Age		
Mean (sd)	69.2 (9.39)	69.2 (8.77)
Gender		
Male	83	80
Female	118	119
Race		
White	183	179
African-American	17	12
American Indian/Alaskan	0	0
Asian	1	6
Native Hawaiian/Pacific Islander	0	0
Other race	0	2
Ethnicity		
Hispanic/Latino	16	28
Not Hispanic/Latino	185	171

Study 526: Subject Demographics (ITT Population)

Parameter	LE Ointment N=203	Vehicle N=202
Age		
Mean	68.3 (9.13)	69.2 (9.36)
Gender		
Male	88	87
Female	115	115
Race		
White	182	178
African-American	13	16
American Indian/Alaskan	2	0
Asian	5	6
Native Hawaiian/Pacific Islander	0	1
Other race	1	1
Ethnicity		
Hispanic/Latino	40	22
Not Hispanic/Latino	163	180

6.1.3 Patient Disposition

The Safety population included all subjects in the ITT population who received at least one dose of study drug. The ITT study population included all subjects who were randomly assigned to

one of the two treatments. The PP study population included all subjects in the ITT population who remained in the study through Visit 5 (POD #8) and who did not deviate from the protocol in any way likely to seriously affect the primary outcome of the study.

Study 525: Patient Disposition

	LE Ointment	Vehicle
Total Number of Subjects Randomized	201	199
Safety Population	201	199
ITT Population	201	199
PP Population	171	170
Reason For Discontinuation		
Withdrawal by subject	0	4
AE	0	1
Investigator Decision	0	1
Failure to follow study protocol	1	0

Study 526: Patient Disposition

	LE Ointment	Vehicle
Total Number of Subjects Randomized	203	202
Safety Population	204	201
ITT Population	203	202
PP Population	180	173
Reason For Discontinuation		
Lost to f/u	1	0
AE	0	2
Travel problem	1	0
Failure to follow study protocol	1	0

During the study, the initiation of rescue therapy and the type of medication given to a subject as rescue therapy was at the Investigator’s discretion. If the Investigator decided that rescue therapy was needed, the following took place:

- Use of study medication was stopped and study drug was collected from the subject. The final tube weight was recorded
- An AE was recorded, ie. worsening inflammation or persistent inflammation
- Rescue therapy was implemented and recorded appropriately on the Concomitant Medication Log, indicating that the medication was being given for rescue therapy
- The subject continued participation in the study and was followed through Visit 7
- For safety purposes, subjects remained in the study and completed all study assessments, even though they were no longer taking study medication

Study 525: Number of Subjects With Rescue Medication Use Prior to Visit (ITT Population)

Subjects With Rescue Medication Use Prior to Visit	LE Ointment N=201	Vehicle N=199
Visit 4 (POD #3)	0	0
Visit 5 (POD# 8)	12	59
Visit 6 (POD# 15)	21	100
Visit 7 (POD# 18)	56	127
Upon Study Exit	68	128

Study 526: Number of Subjects With Rescue Medication Use Prior to Visit (ITT Population)

Subjects With Rescue Medication Use Prior to Visit	LE Ointment N=203	Vehicle N=202
Visit 4 (POD #3)	1	2
Visit 5 (POD# 8)	23	70
Visit 6 (POD# 15)	33	112
Visit 7 (POD# 18)	56	129
Upon Study Exit	62	132

ITT population included patients with missing values and data and from subjects placed on rescue medication who were imputed as failures.

6.1.4 Analysis of Primary Endpoint(s)

The hierarchical primary efficacy endpoints for this study were:

1. The proportion of subjects with complete resolution of anterior chamber cells and flare at Visit 5 (POD# 8)
2. The proportion of subjects with Grade 0 (no pain) at Visit 5 (POD# 8)

The primary analyses of the primary efficacy endpoints first tested the difference in the proportion of subjects with complete resolution of AC cells and flare between treatments at POD# 8 using the Pearson chi-squared statistic. Further, a 95% confidence interval was constructed around the difference in proportions of complete resolution at the POD# 8 visit using asymptotic normal approximations. Treatment success was defined as achieving complete resolution of cells and flare at Visit 5 (POD# 8). Any cell or flare score greater than 0 on Day 8 was judged as a treatment failure. Subjects with missing data on Visit 5 (POD# 8) or subjects who required rescue medication prior to Visit 5 were also judged as failures.

If this first test was statistically significant at the alpha = 0.05 level in favor of LE Ophthalmic Ointment, 0.5%, then the difference in the proportion of subjects with Grade 0 (no pain) between treatments at the POD# 8 visit was tested using the Pearson chi-squared statistic at the alpha = 0.05 level. Pain was judged on a 0-5 scale, and there was no minimum level of baseline pain required for inclusion in the analysis. Treatment success required a subject to have no pain

(Grade 0) on Visit 5 (POD# 8), and any positive value, missing data, or use of rescue medication was judged as a treatment failure for pain. For these ITT analyses, missing data and data from subjects placed on rescue medication prior to the POD# 8 visit were imputed as failures.

Study 525: Primary Efficacy Analysis (ITT Population)

	LE Ointment N=201	Vehicle N=199	P value
Complete resolution of AC cells and flare at Visit 5 (POD #8)			
Yes	48 (23.9%)	27 (13.6%)	0.0022
No	153 (76.1%)	172 (86.4%)	
Subjects without Rescue Medication	139	109	
Subjects with Rescue Medication	12	59	
Subjects with Missing Data	2	4	
Complete resolution of pain at Visit 5 (POD #8)			
Yes	156 (77.6%)	90 (45.2%)	<0.0001
No	45 (22.4%)	109 (54.8%)	
Subjects without Rescue Medication	31	46	
Subjects with Rescue Medication	12	59	
Subjects with Missing Data	2	4	

Study 525: Primary Efficacy Analysis (PP Population)

	LE Ointment N=171	Vehicle N=170	P value
Complete resolution of AC cells and flare at Visit 5 (POD #8)			
Yes	42 (24.6%)	22 (12.9%)	0.0009
No	129 (75.4%)	148 (87.1%)	
Subjects without Rescue Medication	121	98	
Subjects with Rescue Medication	8	50	
Subjects with Missing Data	0	0	
Complete resolution of pain at Visit 5 (POD #8)			
Yes	133 (77.8%)	79 (46.5%)	<0.0001
No	38 (22.2%)	91 (53.5%)	
Subjects without Rescue Medication	30	41	
Subjects with Rescue Medication	8	50	
Subjects with Missing Data	0	0	

Study 526: Primary Efficacy Analysis (ITT Population)

	LE Ointment N=203	Vehicle N=202	P value
Complete resolution of AC cells and flare at Visit 5 (POD #8)			
Yes	64 (31.5%)	23 (11.4%)	0.0001
No	139 (68.5%)	179 (88.6%)	

Subjects without Rescue Medication	114	108	
Subjects with Rescue Medication	23	70	
Subjects with Missing Data	2	1	
Complete resolution of pain at Visit 5 (POD #8)			
Yes	149 (73.4%)	83 (41.1%)	<0.0001
No	54 (26.6%)	119 (58.9%)	
Subjects without Rescue Medication	29	48	
Subjects with Rescue Medication	23	70	
Subjects with Missing Data	2	1	

Study 526: Primary Efficacy Analysis (PP Population)

	LE Ointment N=180	Vehicle N=173	P value
Complete resolution of AC cells and flare at Visit 5 (POD #8)			
Yes	58 (32.2%)	19 (11.0%)	<0.0001
No	122 (67.8%)	154 (89.0%)	
Subjects without Rescue Medication	103	95	
Subjects with Rescue Medication	19	59	
Subjects with Missing Data	0	0	
Complete resolution of pain at Visit 5 (POD #8)			
Yes	133 (73.9%)	71 (41.0%)	<0.0001
No	47 (26.1%)	102 (59.0%)	
Subjects without Rescue Medication	28	43	
Subjects with Rescue Medication	19	59	
Subjects with Missing Data	0	0	

Reviewer's Comment:

When looking at the ITT population for complete resolution of AC cell/flare and pain LE ointment is superior to vehicle in both Studies 525 and 526. The results of the PP analysis are similar to the ITT analysis.

6.1.5 Analysis of Secondary Endpoints(s)

- Proportion of subjects with complete resolution of anterior chamber cells and flare at each visit
- Change from baseline to each follow-up visit in anterior chamber cells and flare

Study 525: Secondary Efficacy Analysis POD #3 (ITT Population)

	LE Ointment N=201	Vehicle N=199	P value
Complete resolution of AC cells and flare at Visit 4 (POD #3)			
Yes	10 (5.0%)	9 (4.5%)	0.8315
No	191 (95.0%)	190 (95.5%)	

Subjects without Rescue Medication	190	187	
Subjects with Rescue Medication	0	0	
Subjects with Missing Data	1	3	
Complete resolution of pain at Visit 4 (POD #3)			
Yes	148 (73.6%)	85 (42.7%)	<0.0001
No	53 (26.4%)	114 (57.3%)	
Subjects without Rescue Medication	52	111	
Subjects with Rescue Medication	0	0	
Subjects with Missing Data	1	3	

Study 525: Secondary Efficacy Analysis POD #15 (ITT Population)

	LE Ointment N=201	Vehicle N=199	P value
Complete resolution of AC cells and flare at Visit 6 (POD #15)			
Yes	84 (41.8%)	30 (15.1%)	<0.0001
No	117 (58.2%)	169 (84.9%)	
Subjects without Rescue Medication	94	65	
Subjects with Rescue Medication	21	100	
Subjects with Missing Data	2	4	
Complete resolution of pain at Visit 6 (POD #15)			
Yes	152 (75.6%)	79 (39.7%)	<0.0001
No	49 (24.4%)	120 (60.3%)	
Subjects without Rescue Medication	26	15	
Subjects with Rescue Medication	21	100	
Subjects with Missing Data	2	5	

Study 525: Secondary Efficacy Analysis POD #18 (ITT Population)

	LE Ointment N=201	Vehicle N=199	P value
Complete resolution of AC cells and flare at Visit 7 (POD #18)			
Yes	86 (42.8%)	39 (19.6%)	<0.0001
No	115 (57.2%)	160 (80.4%)	
Subjects without Rescue Medication	58	29	
Subjects with Rescue Medication	56	127	
Subjects with Missing Data	1	4	
Complete resolution of pain at Visit 7 (POD #18)			
Yes	125 (62.2%)	64 (32.2%)	<0.0001
No	76 (37.8%)	135 (67.8%)	
Subjects without Rescue Medication	19	4	
Subjects with Rescue Medication	56	127	
Subjects with Missing Data	1	4	

Study 526: Secondary Efficacy Analysis POD #3 (ITT Population)

	LE Ointment N=203	Vehicle N=202	P value
Complete resolution of AC cells and flare at Visit 4 (POD #3)			
Yes	10 (4.9%)	9 (4.5%)	0.8020
No	193 (95.1%)	193 (95.5%)	
Subjects without Rescue Medication	191	191	
Subjects with Rescue Medication	1	2	
Subjects with Missing Data	1	0	
Complete resolution of pain at Visit 4 (POD #3)			
Yes	153 (75.4%)	95 (47.0%)	<0.0001
No	50 (24.6%)	107 (53.0%)	
Subjects without Rescue Medication	48	105	
Subjects with Rescue Medication	1	2	
Subjects with Missing Data	1	0	

Study 526: Secondary Efficacy Analysis POD #15 (ITT Population)

	LE Ointment N=203	Vehicle N=202	P value
Complete resolution of AC cells and flare at Visit 6 (POD #15)			
Yes	107 (52.7%)	42 (20.8%)	<0.0001
No	96 (47.3%)	160 (79.2%)	
Subjects without Rescue Medication	60	47	
Subjects with Rescue Medication	33	112	
Subjects with Missing Data	3	1	
Complete resolution of pain at Visit 6 (POD #15)			
Yes	157 (77.3%)	74 (36.6%)	<0.0001
No	46 (22.7%)	128 (63.4%)	
Subjects without Rescue Medication	11	15	
Subjects with Rescue Medication	33	112	
Subjects with Missing Data	2	1	

Study 526: Secondary Efficacy Analysis POD #18 (ITT Population)

	LE Ointment N=203	Vehicle N=202	P value
Complete resolution of AC cells and flare at Visit 7 (POD #18)			
Yes	100 (49.3%)	46 (22.8%)	<0.0001
No	103 (50.7%)	156 (77.2%)	
Subjects without Rescue Medication	45	24	
Subjects with Rescue Medication	56	129	
Subjects with Missing Data	2	3	
Complete resolution of pain at Visit 7 (POD #18)			
Yes	132 (65.0%)	63 (31.2%)	<0.0001

No	71 (35.0%)	139 (68.8%)	
Subjects without Rescue Medication	13	7	
Subjects with Rescue Medication	56	129	
Subjects with Missing Data	2	3	

Study 525: Mean ACR Count (ITT Population)

	Number of Subjects in LE Ointment	LE Ointment	Number of Subjects in Vehicle	Vehicle
Visit 1-Screening	201	0	199	0
Visit 3-POD#1 (sd)	201	3.7 (0.80)	199	3.8 (0.90)
Visit 4-POD #3 (sd)	200	2.7 (1.19)	196	3.3 (1.50)
Visit 5-POD #8 (sd)	199	1.6 (1.35)	195	3.0 (1.79)
Visit 6-POD #15 (sd)	199	1.1 (1.33)	195	2.8 (1.87)
Visit 7-POD #18 (sd)	200	1.2 (1.39)	195	2.7 (1.91)

Study 526: Mean ACR Count (ITT Population)

	Number of Subjects in LE Ointment	LE Ointment	Number of Subjects in Vehicle	Vehicle
Visit 1-Screening	203	0	202	0
Visit 3-POD#1 (sd)	203	3.7 (0.69)	202	3.7 (0.73)
Visit 4-POD #3 (sd)	202	2.5 (1.24)	202	3.1 (1.54)
Visit 5-POD #8 (sd)	201	1.5 (1.47)	201	2.9 (1.79)
Visit 6-POD #15 (sd)	200	1.0 (1.48)	201	2.6 (1.97)
Visit 7-POD #18 (sd)	201	1.1 (1.48)	199	2.6 (2.02)

6.1.6 Other Endpoints

None.

6.1.7 Subpopulations

Reviewer's Comment:

There was not a significant interaction between treatment effect and age, gender, or race.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Only one dosing regimen was studied (QID for 14 days) in both Studies 525 and 526.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Long-term effectiveness was not evaluated for the clinical studies. The duration of treatment for the subjects in these trials was no longer than 14 days. LE ointment is intended for short-term use for the treatment of inflammation and pain following ocular surgery.

6.1.10 Additional Efficacy Issues/Analyses

Analysis of primary efficacy was also performed removing the data from Dr. Kenneth Sall's investigative site. He enrolled 36 patients in Study 525.

Study 525: Primary Efficacy Analysis-Clearing of Cell and Flare at Visit 5 (POD #8) (ITT Population)-Without Dr. Sall's Patients

	LE Ointment N=183	Vehicle N=181	P value
Complete resolution of AC cells and flare at Visit 5 (POD #8)			
Yes	46 (25.1%)	27 (14.9%)	0.0047
No	137 (74.9%)	154 (85.1%)	
Subjects without Rescue Medication	123	91	
Subjects with Rescue Medication	12	59	
Subjects with Missing Data	2	4	
Grade 0 (no pain) at Visit 5 (POD #8)			
Yes	139 (76.0%)	74 (40.9%)	<0.0001
No	44 (24.0%)	107 (59.1%)	
Subjects without Rescue Medication	30	44	
Subjects with Rescue Medication	12	59	
Subjects with Missing Data	2	4	

Reviewer's Comment:

This re-analysis did not significantly change the study results. He did not enroll any patients in Study 526.

7 Review of Safety

Safety Summary

7.1 Methods

7.1.1 Clinical Studies Used to Evaluate Safety

Two clinical studies (Studies 525 and 526) were used to evaluate safety.

7.1.2 Adequacy of Data

Between the 2 studies there were 405 patients in the safety database who received LE ointment.

7.1.3 Pooling Data Across Studies to Estimate and Compare Incidence

Two studies are used to support the safety and efficacy of loteprednol ointment.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Study 525: Treatment Exposure (Safety Population)

	LE Ointment N=201	Vehicle N=199
Days of Exposure		
Mean (sd)	13.2 (3.06)	9.2 (5.10)
Minimum	2	1
Maximum	20	20

Study 526: Treatment Exposure (Safety Population)

	LE Ointment N=204	Vehicle N=201
Days of Exposure		
Mean (sd)	12.7 (3.75)	8.8 (5.15)
Minimum	1	1
Maximum	19	19

7.2.2 Explorations for Dose Response

Only one dosing regimen was studied, Lotemax ointment 0.5% QID.

7.2.3 Special Animal and/or In Vitro Testing

No special animal or in vitro testing was performed.

7.2.4 Routine Clinical Testing

Not applicable.

7.2.5 Metabolic, Clearance, and Interaction Workup

Studies to evaluate metabolism, clearance, and interaction were not performed due to the negligible systemic absorption of LE ointment given by the topical route of administration.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Adverse events for this class of drugs (topical corticosteroids) are well known. Refer to Section 2.2 for currently approved products. Ocular AEs generally associated with ophthalmic steroids include elevated IOP (which may be associated with optic nerve damage and visual acuity and field defects), posterior subcapsular cataract formation, secondary ocular infection from pathogens including herpes simplex, and perforation of the globe where there is thinning of the cornea or sclera. Other reactions include acute anterior uveitis, systemic hypercorticoidism, keratitis, conjunctivitis, corneal ulcers, mydriasis, conjunctival hyperemia, loss of accommodation, and ptosis.

See section 7.4.5 for further detail.

7.3 Major Safety Results

7.3.1 Deaths

There were no deaths in either Study 525 or 526.

7.3.2 Nonfatal Serious Adverse Events

Study 525: Nonfatal SAEs

Patient	Timing of SAE	SAE	Narrative of SAE
Site #262839 Screening #009	Prior to randomization	Retinal tear OS	69 yo female following consent, presented with blurred vision, flashes, floaters, and a spider web-like veil OS for one week. The subject was noted to have a horseshoe tear in the fellow eye without associated retinal detachment. The subject underwent a laser treatment. The outcome is unknown.
Site #453654 Screening #001	Prior to randomization	Kidney failure with strangulated bowel, kidney infection, and sepsis	70 yo male was hospitalized for kidney failure with strangulated bowel, severe kidney infection, and sepsis in the screening phase prior to receiving study drug. The following day the subject underwent an emergency bowel resection then was treated with IV antibiotics and kidney dialysis. The subject made a complete recovery.
Site #508604 Subject #0117	Occurred after randomization	Myocardial infarction	87 yo female with a history of HTN, CAD, and poor circulation in her legs was randomized to the LE ointment group and received study drug

			OD. The following day, the subject was hospitalized with a high fever. Upon further testing she was diagnosed with a MI. No further information was given on the fever condition. While in the hospital, the Investigator stopped the study drug; however, the subject returned for follow-up visits and completed the study.
Site #461665 Subject #0335	Occurred after randomization	Endophthalmitis	79 yo female was randomized to the vehicle group and received the study drug OD. Two days after the first dose was administered, the subject presented with decreased vision OD. The subject's VA was noted as HM and endophthalmitis was diagnosed. The subject was treated with an intravitreal antibiotic injection (vancomycin, ceftazidime, and gentamicin) and sent home with Vigamox, Pred Forte, and atropine. VA was 20/50 upon resolution.
Site #650488 Subject #0357	Occurred after randomization	Myocardial infarction	73 yo male with a history of a prior MI was randomized to the vehicle group and received the study drug OS. Two days later, the subject was hospitalized due to a MI. While recovering at home, the subject was again hospitalized due to SOB secondary to CHF. The subject began lasix and lisinopril and responded well. The events are considered resolved.
Site #505606, Subject #0300	Occurred after randomization	Right shoulder fracture	72 yo male was randomized to the LE ointment group and received the study drug OS. The subject was subsequently hospitalized for a right shoulder fracture after falling. The subject's shoulder required extensive surgical repair. The subject was discharged from the hospital and required to undergo physical therapy. The event is considered ongoing.
Site #946209 Subject #0410	Occurred after randomization	CME OD	60 yo male was randomized to the LE ointment group, and received the study drug OD. The study drug was stopped and the subject was started on rescue therapy for increased post-operative inflammation. Two weeks after final dose of study drug was administered, he experienced blurred and decreased vision OD. The subject was diagnosed with CME. The subject's vision improved following Avastin injection. He exited the study with 1-5 cells and mild flare and a continuing diagnosis of CME. The subject was treated with prednisolone acetate. The event is considered ongoing.
Site #950205 Subject #0106	After exited study	CME OD	70 yo female was randomized to the vehicle group. At the Day 8 visit, the subject was started on rescue therapy (Nevanac TID and Lotemax TID) for persistent post-operative inflammation. The subject exited the study on Day 18; however mild cells (6-15 cells) persisted. The subject returned with decreased vision OD and was diagnosed with CME. She was started on Acular and Pred Forte QID. The subject made a complete recovery.
Site #453654 Subject #0181	After exited study	CME	71 yo male was randomized to the vehicle group. The subject began rescue therapy Pred Forte and Nevanac and on Day 18, the subject's VA was 20/50 and with ongoing residual inflammation. The subject returned to the clinic for a follow-up exam, where his vision dropped two lines to 20/70 and CME was confirmed. The subject continued to take Pred Forte QID and Nevanac QID. The subject also received a 30 mg sub-tenon Kenalog injection. At this visit, the subject's vision was 20/100-1. The subject returned to the clinic subsequently where his VA measured 20/60-1. The subject complained his vision was still blurred; OCT was performed and showed mild CME. The subject continued to take Pred Forte and Nevanac, however, his vision was noted to be slowly improving, and the event was considered to be resolving.
Site #453654	After exited study	CME	65 yo male was randomized to the vehicle group, and received the study

Subject #0282			drug OS. At the Day 3 visit, the subject was started on rescue therapy (Nevanac and Pred Forte) due to increased inflammation. He completed Visit 7, with residual inflammation. The subject was seen for a follow-up visit, at which time VA in the study eye had decreased to 20/70 (from 20/50). An OCT confirmed CME, and the subject was continued on PredForte QID in the study eye and Nevanac QID in the study eye. The subject consulted with a retina specialist and OCT confirmed absence of CME, and VA returned to 20/50. The subject made a complete recovery.
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Study 526: Nonfatal SAEs

Patient	Timing of SAE	SAE	Narrative of SAE
Site #836315 Subject #1177	Occurred after randomization	Blocked coronary artery	76 yo male with a history of hyperlipidemia and HTN was randomized to the LE ointment group and received study drug OS. The subject was hospitalized due to blocked arteries and study medication was discontinued on the same day. The subject underwent stent placement into one of the blocked arteries. The subject was discharged from the hospital and made a complete recovery from the first blocked artery, but was discharged with one blocked artery continuing and taking Plavix and nitroglycerin. Another surgery was to be performed in a couple of weeks. The outcome for this second blocked artery is not recovered.
Site #836315 Subject #1025	Occurred after randomization	Brain tumor	59 yo female was randomized to the vehicle group and received study drug OS. The subject discontinued study medication due to increased inflammation and commenced rescue therapy at Visit 5. At Visit 6, the subject complained of intermittent headaches, a visual disturbance in the study eye, and only being able to see a portion of the eye chart. At this visit, the subject's VA was 20/40 and OCT was normal. Subsequently the subject's visual field test was abnormal, with a visual field cut. A MRI was taken of the subject's brain which showed a large mass that appeared to be centered within the sella turcica which was solid in consistency. Due to the apparent infiltrative nature and encasement of vessels, the event was thought to be most likely representative of a meningioma or perhaps lymphoma rather than a primary pituitary mass. The subject will not undergo surgery in the near future. The event is ongoing.
Site #987168 Subject #1213	Occurred after randomization	Left femoral neck fracture	80 yo female was randomized to the vehicle group and received study drug OD. Subsequently, the subject slipped and fell. The subject was noted to have a left femoral neck fracture and was admitted to the hospital for stabilization the same day. The subject underwent left hip hemiarthroplasty. The subject discontinued the study drug and exited the study. On this same day, the subject developed atrial fibrillation with rapid rate and was given Cardizem iv. The following day, she was converted to sinus rhythm and was given additional doses of Cordarone.
Site #990165 Subject #1232	Occurred after randomization	Worsening of diabetic foot	66 yo male with a history of DM and left foot gangrene was randomized to the vehicle group and received study drug OS. At Visit 6, the subject presented with worsening of diabetic foot and was hospitalized. The event is considered to be resolving.

7.3.3 Dropouts and/or Discontinuations

Study 525: Primary Reason for Subject Discontinuation

	LE Ointment N=201	Vehicle N=199
Withdrawal by subject	0	4
AE	0	1 *
Investigator decision	0	1
Failure to follow study procedures	1	0

*At site #461665, subject ID #0335, a 79-year-old white female, who enrolled in the study on 1/14/09, discontinued on 1/23/09 due to an SAE (severe endophthalmitis,). See section 7.3.2 for more details.

Study 526: Primary Reason for Subject Discontinuation

	LE Ointment N=203	Vehicle N=202
Lost to f/u	1	0
AE	0	2 *
Failure to follow study procedures	1	0
Travel problem	1	0

*At site #987168, subject ID #1213, an 80 yo female subject, who began to receive treatment on 10/31/08, had an SAE (severe fall of unknown cause and broken hip). This subject discontinued the study on 11/11/08 due to the SAE. At site #990165, subject ID #1232, a 66 yo white male, whose screening visit was 10/28/08, discontinued due to an SAE (worsening diabetic foot ulcer) and discontinued on 11/19/08.

7.3.4 Significant Adverse Events

See section 7.3.2.

7.3.5 Submission Specific Primary Safety Concerns

None.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Treatment-emergent AEs were defined as any AE collected with a start date on or following the first administration of study drug or any AE collected with a start date on or after the day of enrollment that worsened or persisted to the point the Investigator deemed it to be an AE.

Study 525: Ocular Treatment-Emergent AEs in >3% of Study Eyes (Safety Population)

	LE Ointment N=201	Vehicle N=199
Total Number of AEs	194	340
Number of Subjects with at Least 1 AE	110 (54.7%)	161 (80.9%)

AC Inflammation	61	106
Photophobia	17	19
Eye pain	8	26
Iritis	11	19
Conjunctival hyperemia	10	15
Eye pruritis	5	16
Lacrimation increased	6	14
Corneal edema	8	11
AC cell	5	10
Ciliary hyperemia	5	10
Ocular hyperemia	5	10
Vision blurred	5	7
AC flare	2	9
Visual acuity reduced	4	7
Dry eye	3	6
FBS	3	6
IOP increased	3	7

Overall, 534 ocular TEAEs were reported. The percentage of subjects who had at least one ocular TEAE in the LE Ointment treatment group (110, 54.7%) compared to those in the vehicle treatment group (161, 80.9%), $p < 0.0001$.

Study 525: Non-ocular Treatment-Emergent AEs in >1% of Study Eyes (Safety Population)

	LE Ointment N=201	Vehicle N=199
Total Number of AEs	23	14
Number of Subjects with at Least 1 AE	16 (8.0%)	9 (4.5%)
Headache	4	2
Drug hypersensitivity	2	1
Nasopharyngitis	2	0
Cough	2	0

Study 526: Ocular Treatment-Emergent AEs in >3% of Study Eyes (Safety Population)

	LE Ointment N=204	Vehicle N=201
Total Number of AEs	119	241
Number of Subjects with at Least 1 AE	81 (39.7%)	151 (75.1%)
AC Inflammation	49	94
Eye pain	7	17
Corneal edema	10	12
Conjunctival hyperemia	6	15
Ciliary hyperemia	5	13
Photophobia	5	12
Iritis	4	12

Uveitis	4	10
AC cell	5	6

Overall, 360 ocular TEAEs were reported. The percentage of subjects who had at least one ocular TEAE in the LE Ointment treatment group (81, 39.7%) compared to those in the vehicle treatment group (151, 75.1%), $p < 0.0001$.

Study 526: Non-ocular Treatment-Emergent AEs in >1% of Study Eyes (Safety Population)

	LE Ointment N=204	Vehicle N=201
Total Number of AEs	7	11
Number of Subjects with at Least 1 AE	5 (2.5%)	9 (4.5%)
Headache	2	3

7.4.2 Laboratory Findings

Not performed.

7.4.3 Vital Signs

Not performed.

7.4.4 Electrocardiograms (ECGs)

Not performed.

7.4.5 Special Safety Studies

Corticosteroids have a known risk of increasing IOP and therefore IOP was monitored at every visit.

Study 525: IOP Change From Baseline Prior to Rescue Medication Use Visit 7 (Safety Population)

	LE Ointment N=146	Vehicle N=66
Visit 7 (POD# 18)		
Mean (sd)	-1.9 (3.75)	-1.2 (4.28)
<=-15	1	1
-14 to -10	4	1
-9 to -5	22	10
-4 to 0	90	32
1 to 4	24	19
5 to 9	5	2

Clinical Review
 Sonal D. Wadhwa, MD
 NDA 200-738
 Lotemax (loteprednol etabonate ophthalmic ointment) 0.5%

10 to 14	0	1
15 to 19	0	0
>=20	0	0

Study 525: IOP Measurement Prior to Rescue Medication Use (Safety Population)

	LE Ointment N=201	Vehicle N=199
Visit 3 (POD# 1)		
Mean (sd)	15.9 (3.77)	16.1 (4.66)
<=5	0	0
6-14	68	79
15-21	123	101
22-29	8	15
>=30	2	4
	LE Ointment N=146	Vehicle N=66
Visit 7 (POD# 18)		
Mean (sd)	14.0 (2.96)	14.3 (2.62)
<=5	0	0
6-14	86	35
15-21	60	31
22-29	0	0
>=30	0	0

Study 525: Highest IOP at Any Visit (Safety Population)

	LE Ointment N=201	Vehicle N=197
Mean (sd)	15.9 (3.15)	14.3 (3.41)
<=5	0	1
6-14	58	99
15-21	139	94
22-29	3	3
>=30	1	0
Change From Baseline Worst Visit (Highest IOP)		
Mean (sd)	0.0 (3.02)	-1.8 (4.72)
<=-15	0	3
-14 to -10	1	6
-9 to -5	11	37
-4 to 0	106	90
1 to 4	68	48
5 to 9	15	12
10 to 14	0	1
15 to 19	0	0
>=20	0	0

Study 526: IOP Change From Baseline Prior to Rescue Medication Use (Safety Population)

	LE Ointment N=147	Vehicle N=68
Visit 7 (POD# 18)		
Mean (sd)	-1.7 (3.47)	-1.0 (4.39)
<=-15	0	0
-14 to -10	2	2
-9 to -5	26	15
-4 to 0	91	26
1 to 4	22	17
5 to 9	5	8
10 to 14	1	0

Study 526: IOP Measurement Prior to Rescue Medication Use (Safety Population)

	LE Ointment N=204	Vehicle N=201
Visit 3 (POD# 1)		
Mean	15.8 (3.36)	15.8 (4.13)
<=5	0	0
6-14	67	72
15-21	131	114
22-29	6	14
>=30	0	1
	LE Ointment N=147	Vehicle N=68
Visit 7 (POD# 18)		
Mean (sd)	14.3 (3.05)	14.6 (3.15)
<=5	0	0
6-14	79	35
15-21	68	31
22-29	0	2
>=30	0	0

Study 526: Highest IOP at Any Visit (Safety Population)

	LE Ointment N=203	Vehicle N=199
Mean (sd)	15.9 (2.77)	14.9 (3.12)
<=5	0	0
6-14	63	84
15-21	136	112
22-29	4	3
>=30	0	0
	LE Ointment N=203	Vehicle N=199
Change From Baseline Worst Visit (Highest IOP)		
Mean (sd)	0.1 (3.34)	-0.9 (4.24)

<=-15	0	1
-14 to -10	0	4
-9 to -5	19	26
-4 to 0	95	99
1 to 4	72	48
5 to 9	14	21
10 to 14	3	0
15 to 19	0	0
>=20	0	0

7.4.6 Immunogenicity

Not applicable.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Not performed.

7.5.2 Time Dependency for Adverse Events

Not performed.

7.5.3 Drug-Demographic Interactions

The incidence of treatment-emergent ocular and non-ocular AEs prior to rescue medication use were compared between the LE Ointment and vehicle treatment groups for the following subpopulations: age (< 65, 65 to <75 and \geq 75 years), gender, and race (white and non-white). These rates were consistent with rates observed in the overall safety population.

7.5.4 Drug-Disease Interactions

LE ointment was evaluated for the treatment of post-surgical ocular inflammation with no drug-disease interaction analysis.

7.5.5 Drug-Drug Interactions

No studies were conducted to evaluate a drug-drug interaction between LE ointment and any of the concomitant medications allowed in those studies. Drug interactions, if any, are expected to be similar to those for other corticosteroids. The extremely limited systemic absorption of LE ointment would limit the potential for drug interaction.

7.6 Additional Safety Explorations

7.6.1 Human Carcinogenicity

Because of the low expected absorption of LE in topical preparations, no carcinogenicity studies were conducted.

7.6.2 Human Reproduction and Pregnancy Data

This drug has not been tested in pregnant women.

7.6.3 Pediatrics and Effect on Growth

This drug was not tested on a pediatric population. Height and weight data were not collected as part of this protocol.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

LE ointment is a non-narcotic and does not have abuse potential.

7.7 Additional Submissions

Not applicable.

8 Post-marketing Experience

Lotemax ointment is not currently marketed in any country. Loteprednol etabonate is the active pharmaceutical ingredient in LE ointment and is the same sterile form of the API that has been marketed for over a decade in the following drug products:

- Lotemax - Loteprednol Etabonate Ophthalmic Suspension, 0.5%, marketed since March 1998
- Alex - Loteprednol Etabonate Ophthalmic Suspension, 0.2%, marketed since March 1998
- Zylet - Loteprednol Etabonate and Tobramycin Ophthalmic Suspension 0.5%, 0.3% launched December 2004

In addition to the US, Lotemax, Alex, Zylet have been approved in countries throughout Latin America, Europe, and Asia/Pacific regions. Recent shipped quantities of Lotemax, Alex, and Zylet are shown below. Within approximately the first six months of 2009 there have been over (b) (4) of product containing LE sold. Assuming that each unit represents treatment for one patient, as this is the usual quantity prescribed per treatment, over (b) (4) have been treated within approximately the first six months of 2009.

Product	Dates	Total Units
Lotemax	2/1/09-7/31/09	(b) (4)
Alrex	1/1/09-6/30/09	(b) (4)
Zylet	1/1/09-6/30/09	(b) (4)

9 Appendices

9.1 Literature Review/References

A pub med search did not reveal any new information on loteprednol ointment.

9.2 Advisory Committee Meeting

No Advisory Committee Meeting was held. There were no new issues raised in the review of the application which were thought to benefit from an Advisory Committee Meeting.

3 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

Reviewer's Comments:

The applicant submitted carton and container labels and package insert on 12/23/09. The labeling should be revised as follows:

1.  (b) (4)
2. *As currently presented, the manufacturer statement 'Bausch & Lomb' is as prominent the proprietary name. The most prominent information on the principal display panel should be the proprietary name immediately followed by the established name, dosage form and strength. Decrease the prominence of the manufacturer statement and relocate it away from the proprietary name in the carton and container.*
3. *As currently presented the carton labeling lacks the expiration date and lot number. Include this information on all carton labeling.*
4. *Revise so that the established name is printed in letters that are at least half as large as the letters comprising the proprietary name, and the established name has a prominence commensurate with the prominence with which such proprietary name, taking into account all pertinent factors, including typography, layout, contrast, and other printing features in accordance with 21 CFR 201.10 (g)(2).*
5. *Increase the prominence of the product strength. The most prominent information on the principal display panel should be the proprietary name immediately followed by the established name, dosage form and strength.*
6. *Increase the prominence of the statement 'Sample-Not for Resale' located on the principal display panel.*
7.  (b) (4)
8. *Revise the statement "Do not use if bottom ridge of tube cap is exposed".*

5 Page(s) of Draft Labeling Withheld in Full as b4 (CCI/TS)
immediately following this page

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SONAL D WADHWA
09/27/2010

WILLIAM M BOYD
09/27/2010